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RESPIRATORY CARE

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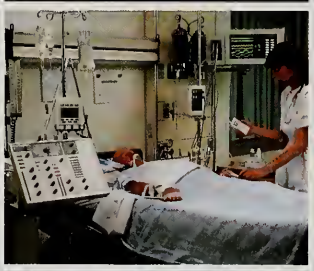

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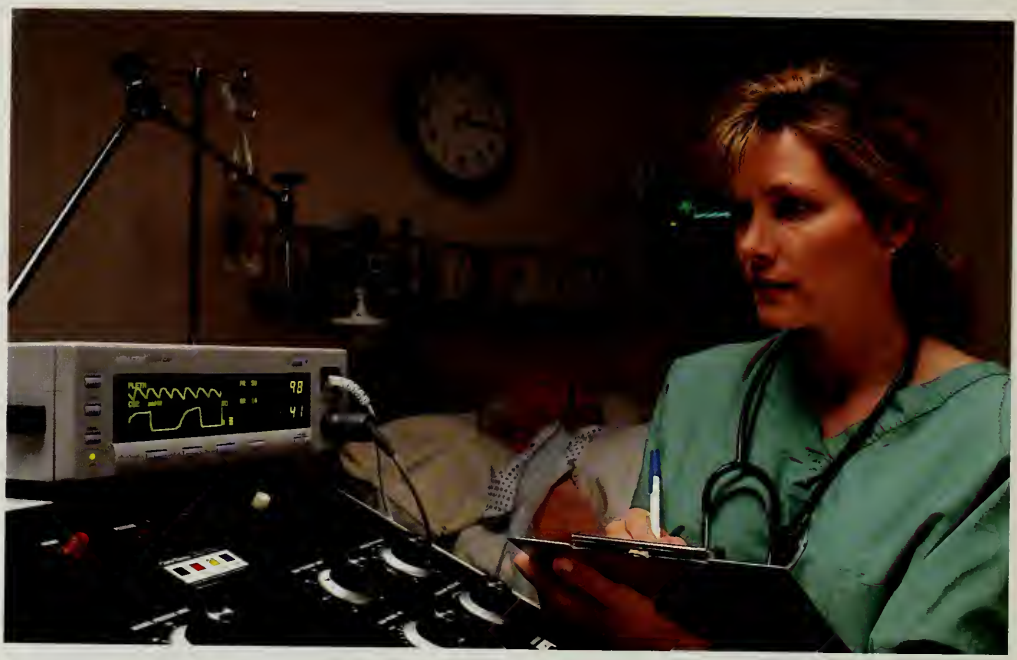

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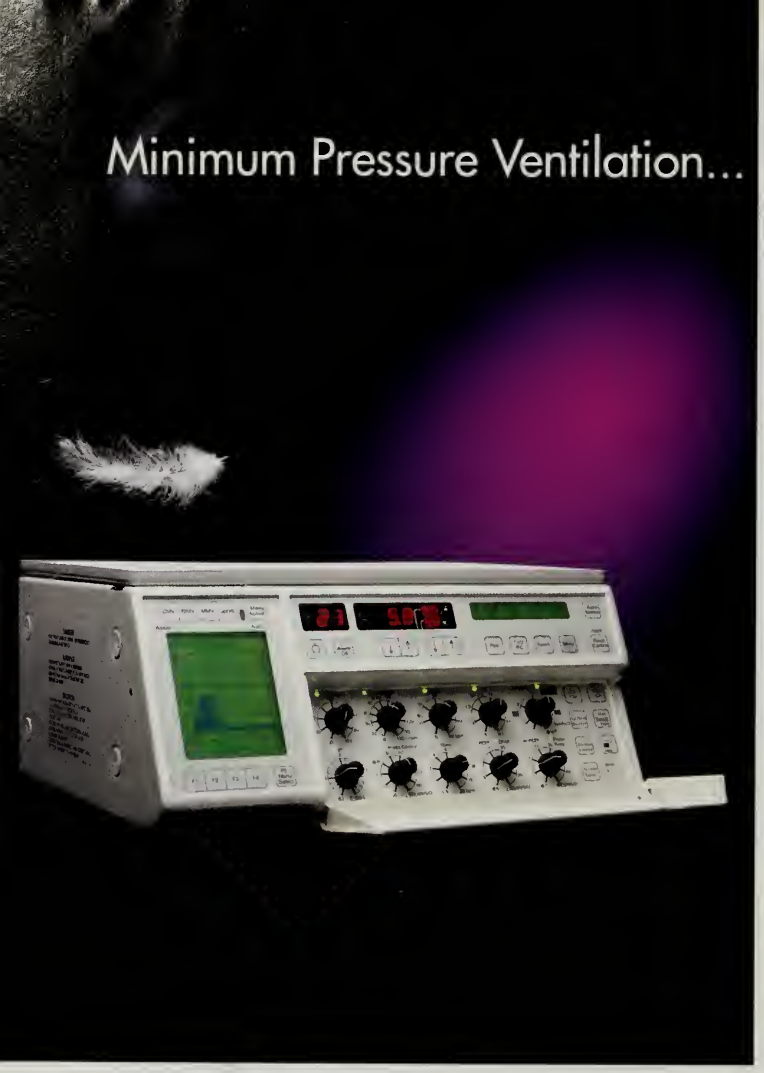

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Diaphragmatic Pacing (clinical commentary)—J Moxham, JM Shneerson. Am Rev Respir Dis 1993;148:533.

Barotrauma: Detection, Recognition, and Management (review)—TW Marcy. Chest 1993;104:578.

Does the Bronchoscope Propagate Infection? (review)—UBS Prakash. Chest 1993;104:552.

Sedation, Analgesia, and Paralysis in the Intensive Care Unit (review)—AP Wheeler. Chest 1993;104:566.

Clinically Available New Strategies for Mechanical Ventilatory Support (review)—NR MacIntyre. Chest 1993; 104:560.

Influence of Atelectasis on Pulmonary Function after Coronary Artery Bypass Grafting—FS Vargas, A Cukier, M Terra-Filho, W Hueb, LR Teixeira, RW Light. Chest 1993;104:434.

The purpose of this study was to determine the influence of atelectasis on pulmonary function 6 days following coronary artery bypass grafting (CABG). After 6 days, 30 patients had normal chest radiographs, 38 had atelectasis, and 57 had pleural changes. In 11 patients, atelectasis only was observed in the radiograph, and in 27 it was in combination with pleural changes. The decrease in FVC and FEV_1 in the patients with atelectasis was 33.4 and 33.5% in the SVG (saphenous vein graft) group and 34.8 and 34.3% in the IMA (internal mammary artery) group, while in those patients with a normal radiograph, the decrements were 26.3 and 26.9% in SVG group and 26.1 and 26.9% in IMA group, respectively. Thus, patients with atelectasis on the 6th postoperative day have a larger decrement in pulmonary function post-CABG than the patients with normal chest radiograph and this reduction reflects a higher degree of thoracic trauma.

Improving Inhaler Adherence in a Clinical Trial through the Use of the Nebulizer Chronolog—MA Nides, DP Tashkin, MS Simmons, RA Wise, VC Li, CS Rand. Chest 1993;104:501.

This study examined whether utilizing an electronic medication monitor (Nebulizer Chronolog) to provide participants with detailed feedback on their metered-dose inhaler (ipratropium bromide or placebo) usage patterns would result in closer adherence to the prescribed regimen of two inhalations three times daily compared to a control group not receiving feedback. Adherence was also measured by canister weighing and self-report. Two-hundred fifty-one consecutive special intervention participants from the University of California, Los Angeles, and Johns Hopkins University centers of a National Heart, Lung, and Blood Institute-sponsored clinical trial were enrolled in this ancillary study. Compared to controls, feedback participants at the 4-month follow-up adhered more closely to the prescribed three sets per day (mean 1.95 vs 1.65) and used the prescribed two actuations in a greater percentage of sets (80% vs 60.3%). These results indicate that electronic monitoring of metered-dose inhaler use with a Nebulizer Chronolog in a clinical trial not only provides a more accurate assessment of adherence to prescribed inhaler use, but also enhances adherence when participants are given feedback of the monitoring results.

Trial of Standard versus Modified Expiration to Achieve End-of-Test Spirometry Criteria—JK Stoller, S Basheda, D Laskowski, M Goormastic, K McCarthy. Am Rev Respir Dis 1993;148:275.

To assess whether satisfying American Thoracic Society (ATS) end-of-test spirometry criteria can be enhanced by modifying the patient's expiratory technique, we conducted a cross-over trial of two expiratory techniques in 48 patients with a range of pulmonary functions (Group 1, n = 12: $FEV_1/FVC < 0.45$; Group 2, n = 11: FEV_1/FVC, 0.45 to 0.60; Group 3, n = 16: FEV_1/FVC, 0.61 to 0.74; Group 4, n = 9: $FEV_1/FVC \geq 0.75$). After randomizing the order of testing, each patient performed three exhalations using a "standard" forced expiratory maneuver and a modified expiratory

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Hemodynamic and Gas Exchange Responses to Infusion of Acetylcholine and Inhalation of Nitric Oxide in Patients with Chronic Obstructive Lung Disease and Pulmonary Hypertension—S Adnot, C Kouyoumdjian, C Defouilloy, P Andrivet, S Sediame, R Herigault, M-D Fratacci. Am Rev Respir Dis 1993; 148:310.

To investigate endothelium-dependent and endothelium-independent nitric oxide (NO) mediated pulmonary vasodilation in patients with chronic obstructive lung disease (COLD), we examined the responses to incremental infusion rates of acetylcholine (ACh) or inhaled NO on hemodynamics and gas exchange. In 13 patients, ACh (15 mg/min) de-

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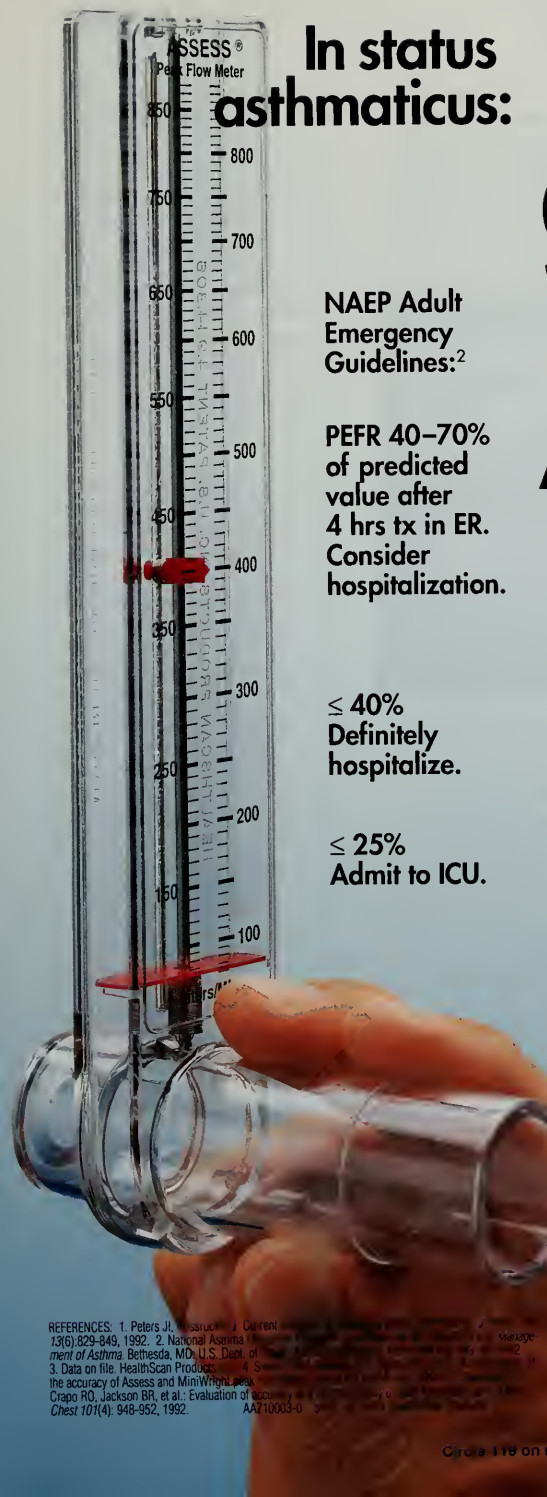

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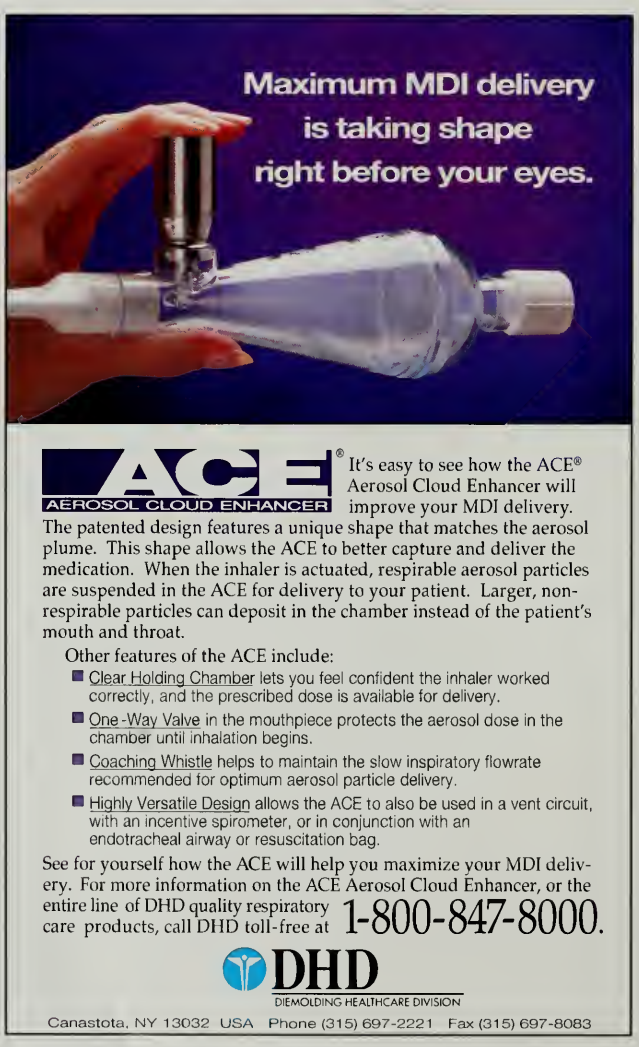
creased pulmonary artery pressure (Ppa) from 31 ± 1 to 28 ± 1 mm Hg ($p < 0.01$) and systemic arterial pressure while increasing cardiac index from 3.7 ± 0.4 to 4.7 ± 0.4 L/min/m^2 ($p < 0.01$). Inhaling 40 parts per million (ppm) NO decreased Ppa from 32 ± 1 to 26 ± 1 mm Hg ($p < 0.001$) with no associated hemodynamic change. ACh reduced P_{aO_2} from 57 ± 3 to 48 ± 2 mm Hg ($p < 0.01$) and increased venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$) from 35 ± 3 to 45 ± 3% ($p < 0.01$). Inhaling 40 ppm NO increased P_{aO_2} from 57 ± 3 to 60 ± 3 mm Hg ($p < 0.01$) and decreased $\dot{Q}_{VA}/\dot{Q}_T$ from 36 ± 3 to 32 ± 3% ($p < 0.01$). Pulmonary vascular resistance changes were similar in response to 40 ppm NO or 15 mg/min ACh. In COLD patients, ACh produces both pulmonary and systemic vasodilation but impairs arterial oxygenation, whereas inhaled NO induces selective pulmonary vasodilation while improving gas exchange. The resistance to ACh in some patients could be related to pulmonary endothelial dysfunction.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Atrial Natriuretic Peptide Improves Pulmonary Gas Exchange in Subjects Exposed to Hypoxia—RGJ Westendorp, AN Roos, HG Vd Hoeven, MY Tjiong, R Simons, M Frölich, et al. Am Rev Respir Dis 1993;148:304.

Atrial Natriuretic Peptide (ANP) is secreted in response to hypoxia and pulmonary vasoconstriction. The hormone modulates pulmonary vascular tone in vivo and decreases pulmonary edema in isolated lungs exposed to several toxic agents. In addition, ANP improves the barrier function of endothelial cell monolayers in vitro. The plasma levels of ANP are elevated in patients with high-altitude pulmonary edema. We hypothesized that under these circumstances, ANP improves pulmonary gas exchange by attenuating the transvascular permeation of plasma (water). Therefore, we studied the effect of low-dose ANP in 11 healthy mountaineers exposed to hypoxia in a single-blind, placebo-controlled, cross-over design. During four 1-h periods, the subjects were stepwise exposed to decreasing barometric pressure, with a minimum of 456 mm Hg (simulated altitude, 4,115 m). Infusion of 5 ng/kg/min human-ANP increased the plasma ANP concentrations approximately twofold. The plasma concentrations of cyclic GMP, which is the

second messenger of ANP, rose approximately threefold. Infusion of ANP did not affect the hemodynamic or ventilatory response to hypoxia. The hemoglobin concentration, however, rose from 9.0 ± 0.1 to 9.4 ± 0.1 mmol/L ($p < 0.01$) during ANP infusion but not during placebo infusion. The change in plasma volume calculated from this hemoconcentration indicated that approximately 10% of the plasma volume had permeated into the interstitium. Despite the observed whole-body hemoconcentration, oxygen saturation was significantly higher during ANP infusion than during placebo infusion (84.7 ± 1.7 versus 79.6 ± 1.8%, $p < 0.05$), and the alveolar-arterial oxygen difference was significantly lower (3.5 ± 0.7 versus 7.3 ± 0.8 mm Hg, $p < 0.01$). The increase in arterial oxygen saturation was inversely correlated with the alveolar-arterial oxygen difference ($r = 0.66$, $p < 0.05$), which is compatible with the hypothesis that oxygen saturation increased as a result of an improved pulmonary gas exchange.

Factors Determining Pulmonary Function in Adolescent Idiopathic Thoracic Scoliosis—C Kearon, GR Viviani, A Kirkley, KJ Killian. Am Rev Respir Dis 1993;148:288.

Adolescent idiopathic thoracic scoliosis may lead to severe pulmonary impairment and early death, but the responsible factors are poorly understood; pulmonary function is only weakly related to the angle of scoliosis. We performed a cross-sectional study using multivariate analysis to identify the individual and additive influence of different features of spinal deformity and nonstructural factors on pulmonary impairment. Pulmonary function was assessed by measuring lung volumes and diffusing capacity, with a *priori* selection of vital capacity (expressed as percentage of predicted, % VC) as the primary index of pulmonary impairment. Radiologic and physiologic measurements were made independently in 66 subjects who had not previously had spinal surgery. Angle of scoliosis ($p = 0.01$) was one of four features of spinal deformity associated with reduced % VC: greater number of vertebrae involved ($p = 0.007$), cephadal location of the curve ($p = 0.04$), and loss of the normal thoracic kyphosis ($p = 0.002$) made an equal and additive contribution to pulmonary impairment. Spinal deformity led to reductions in VC, primarily by reducing TLC. Spinal column rotation, respiratory muscle strength, and duration of the curvature were not related to pulmonary function ($p > 0.05$). We conclude that features of the spinal deformity are the major determinants of pulmonary impairment in idiopathic thoracic scoliosis but that the relationship between deformity and impairment is complex. The severity of pulmonary impairment cannot be inferred to a clinically useful extent from the angle of scoliosis alone.

Factors Influencing Work Capacity in Adolescent Idiopathic Thoracic Scoliosis—C Kearon, GR Viviani, KJ Killian. Am Rev Respir Dis 1993;148:295.

The factors contributing to reduced work capacity (disability) in adolescent idiopathic thoracic scoliosis are poorly understood. We performed a cross-sectional study using multivariate analysis to identify the individual and additive influence of spinal deformity, pulmonary impairment, and muscular function on work capacity in 79 subjects with idiopathic scoliosis (angle of scoliosis 45 ± 18.5°, SD). Work capacity was measured using an incremental cycle test, and the cardiorespiratory response to exercise was compared with that of normal subjects. Work capacity was reduced (% Wcap, 86%; 95% CI 81.9 to 89.7), indicating significant disability. The % Wcap was unrelated to the nature and extent of spinal deformity ($p > 0.05$). Leg muscularity and pulmonary impairment had an additive influence on work capacity, the relationship with muscularity being the stronger of the two. Independently of muscularity and pulmonary impairment, a high heart rate response at submaximal work rates was also associated with a reduced work capacity. Ventilation was normal for metabolic demands. During exercise, the tidal volumes of scoliotic subjects were reduced in proportion to the vital capacity. We conclude that disability occurs with mild to moderate idiopathic scoliosis and appears to be related to a combination of reduced ventilatory capacity, reduced muscularity, and cardiovascular deconditioning. These findings suggest that physical activity should be encouraged in subjects with idiopathic scoliosis to maintain peripheral muscle and cardiovascular conditioning, thereby minimizing disability.

Role of Hyperventilation in the Pathogenesis of Central Sleep Apneas in Patients with Congestive Heart Failure—M Naughton, D Benard, A Tam, R Rutherford, TD Bradley. Am Rev Respir Dis 1993; 148:330.

Periodic breathing with central apneas during sleep is typically triggered by hypocapnia resulting from hyperventilation. We therefore hypothesized that hypocapnia would be an important determinant of Cheyne-Stokes respiration with central sleep apnea (CSR-CSA) in patients with congestive heart failure (CHF). To test this hypothesis, 24 male patients with CHF underwent overnight polysomnography during which transcutaneous P_{CO_2} (P_{tcCO_2}) was measured. Lung to ear circulation time (LECT), derived from an ear oxim-

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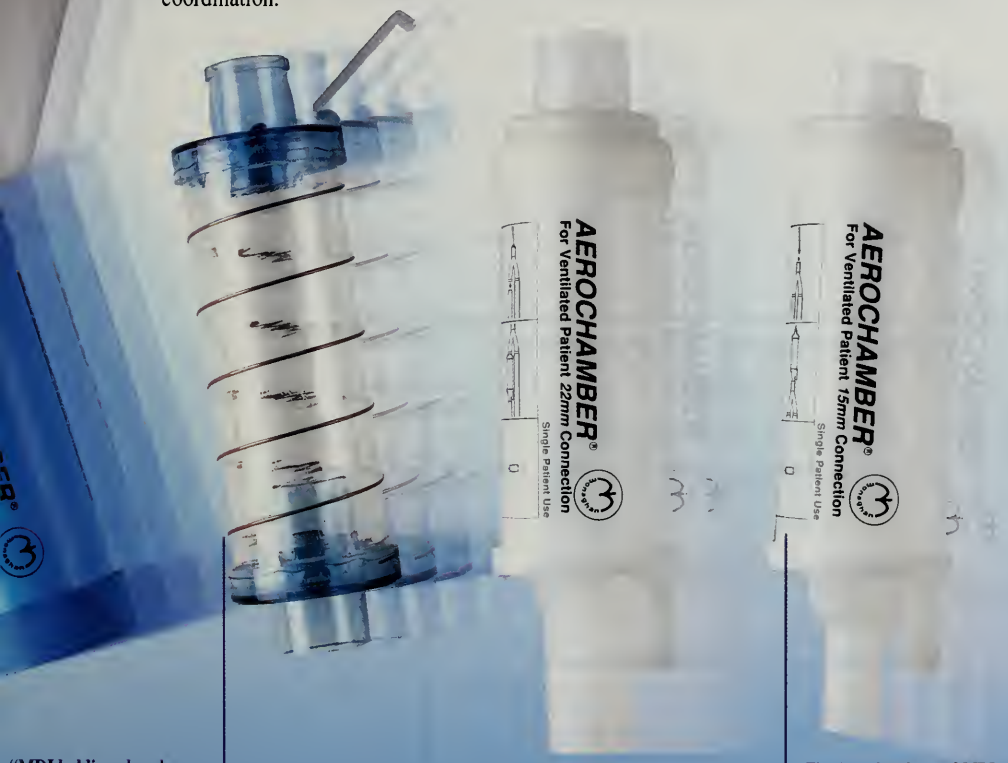

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Aerosol Consensus Statement, Respiratory Care, Sept.'91, Vol. 36 No. 9

"This study has demonstrated that a MDI plus aerosol holding chamber delivers a nearly fivefold greater dose of aerosolized drug to the lungs in comparison with a jet nebulizer in patients receiving mechanical ventilation." H.D. Fuller, M.B. Dolovich, G. Posmituck, W. Wong Pack, and M.T. Newhouse. Pressurized Aerosol versus Jet Aerosol Delivery to Mechanically Ventilated Patients. Am Rev Respir Dis 1990; 141:440-444.

"The Aerochamber and MDI appears to be a highly efficient method of budesonide delivery to ventilated infants." J. Grigg, et al Hammersmith Hospital, London, England. Delivery of therapeutic aerosols to intubated babies. Archives of Disease in Childhood 1992; 67: 25-30

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eter as an estimate of circulatory delay, and CSR-CSA cycle length were determined. Patients were divided into a CSR-CSA group (n = 12, mean ± SEM of 49.2 ± 6.3 central apneas and hypopneas per h sleep) and a control group without CSR-CSA (n = 12, 4.9 ± 0.8 central apneas and hypopneas per h sleep). There were no significant differences in left ventricular ejection fraction, awake P_{aO_2}, mean nocturnal S_{aO_2}, or LECT between the two groups. In contrast, the awake P_{aCO_2} and mean sleep P_{tcCO_2} were significantly lower in the CSR-CSA group than in the control group (33.0 ± 1.2 versus 37.5 ± 1.0 mm Hg, $p < 0.01$, and 33.2 ± 1.2 versus 42.5 ± 1.2 mm Hg, $p < 0.0001$, respectively). Neither group had significant awake or sleep-related hypoxemia. In addition, CSR-CSA cycle length correlated with LECT ($r = 0.939$, $p < 0.001$). We conclude that (1) hypocapnia is an important determinant of CSR-CSA in CHF and (2) circulatory delay plays an important role in determining CSR-CSA cycle length.

Tracheal Gas Insufflation Augments CO_2 Clearance during Mechanical Ventilation—SA Ravenscraft, WC Burke, A Nahum, AB Adams, G Nakos, TW Marcy, JJ Marini. Am Rev Respir Dis 1993; 148:345.

A technique that improves the efficiency of alveolar ventilation should decrease the pressure required and reduce the potential for lung injury during mechanical ventilation. Alveolar ventilation may be improved by replacing a portion of the anatomic dead space with fresh gas via an intratracheal catheter. We studied the effect of intratracheal gas insufflation as an adjunct to volume-cycled ventilation in eight sedated, paralyzed patients with a variety of lung disorders. Continuous flows of 2, 4, and 6 L/min were delivered through a catheter positioned 1 or 10 cm above the carina. Carbon dioxide production, inspiratory minute ventilation, and peak and mean airway pressures did not change over the range of flows tested. P_{aCO_2} and dead space volume/tidal volume decreased significantly as joint functions of catheter flow and position ($p < 0.001$). The highest catheter flow (6 L/min) and most distal catheter position (1 cm above the carina) were the most effective combination tested, averaging a 15% reduction in P_{aCO_2} (range 9 to 23%). Certain characteristics of the expiratory capnogram were helpful in predicting the observed reduction in P_{aCO_2}. Tracheal gas insufflation may eventually prove a useful adjunct to a pressure-targeted strategy of ventilatory management (in either volume-cycled or pressure-controlled modes), particularly when the total dead space is heavily influenced by its anatomic component.

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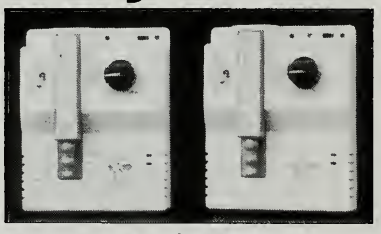

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Combined Drug Therapy in Asthma

Certain diseases, such as deficiency states or those caused by a single pathogen, may be treatable with a single drug. From this, the ancient dictum "one disease, one remedy" has persisted in medical lore. The implication is that accurate diagnosis will narrow the choice of treatment perhaps to a single agent. However, diagnostic entities are human constructs, limited by the acuity of our clinical observations and our understanding of pathologic processes. For example, essential hypertension is frequently diagnosed, but no causative process for the condition has yet been defined. The consequence is the prescription of multiple remedies, which, in refined form, is a stepped approach—each new medication added when the previous regimen is shown to be inadequate. The optimum treatment of many conditions can involve the simultaneous or serial employment of several drugs. In cancer chemotherapy and for many infectious diseases, multiple drug therapy has become the standard of practice.

The necessity for multiple agents is further compounded when the patient has more than one disease. In an aging population, it is common to find individuals taking more than a dozen drugs. Hospitalized patients are often on 6 or more, and the critically ill may be receiving more than 20. A large literature has developed on the subject of drug interactions, the pitfalls that can be anticipated when drugs are combined in the treatment program.

Asthma is a condition whose etiology is often obscure, with many contributory factors, several bronchoconstrictor substances, and a variety of clinical courses. Multiple drug therapy is commonly required for effective management. In the past decade, a prominent shift of therapeutic emphasis has occurred—from a predominantly bronchodilator regimen to the use of drugs to suppress the underlying inflammatory process. For acute treatment of the asthma episode, however, ß-adrenoceptor agonists and antimuscarinic agents remain the first drugs of choice. The properties and uses of these compounds are reviewed by Howder in this issue of the Journal.[1] A valuable part of the paper concerns their employment in combination. Nine studies are cited in which a $ß_2$ agonist and ipratropium bromide were given. Although the effects of the combined drugs are assumed to be additive, the sequence in which they are administered is important.

Autoradiographic studies have shown that the density of muscarinic receptors is greatest in the large central bronchioles, diminishing progressively in the smaller airways. In contrast, $ß_2$-adrenoceptors show a higher density in the small peripheral bronchioles. Thus, it follows that ipratropium bromide preferentially relaxes the smooth muscle of the larger central airways, whereas the effect of $ß_2$ agonists is directed more to the small bronchioles. If this is true, then ipratropium aerosol administered first will open the larger bronchioles, providing better access to the smaller ones when the $ß_2$ agonist is given subsequently. This order of administration is emphasized in the review; giving the $ß_2$ agonist before the ipratropium was found to be less effective. When the studies were extended to include patients with chronic bronchitis, ipratropium tended to become the primary drug of choice because of its antisecretory activity.

When drugs are given concurrently, the potential for interaction with untoward consequences is an important consideration. Also, the order of administration of the agents can affect the therapeutic outcome. Often these interactions are unforeseen and are discovered fortuitously. Where combined therapy is indicated, the value of careful clinical documentation cannot be overestimated, and surveys of these observations can be significant contributions to medical progress. The bronchodilator review in this issue is an excellent example.

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REFERENCE

1. Howder CL. Antimuscarinic and $ß_2$-adrenoceptor bronchodilators in obstructive airways disease. Respir Care 1993;38(12):1364-1388.

A Question of Ethics: Funding of Continuing Education

In 1990 when Senator Edward Kennedy's congressional committee held a series of hearings on drug company promotional practices, many health professionals (and much of the public) first became aware of the questionable ethics of continuing education funding by companies standing to profit from such activities. Subsequently, Andy Rooney did a piece for "60 Minutes" in which he highlighted giveaway programs run by pharmaceutical companies. *Consumer Reports*[1] ran a feature story about the takeover of continuing education of health professionals by commercial interests. These actions, coupled with a revelation that profit margins for the pharmaceutical industry were as much as 17% and prescription prices had jumped 150% in 10 years,[2] prompted the Food and Drug Administration (FDA) to prepare guidelines for sponsors of continuing education activities.

The FDA was concerned that commercial sponsorship of continuing education activities by drug and medical equipment manufacturers was really nothing more than promotional activity for their products. The FDA was concerned that companies might influence content of educational programs—not only directly by the selection of speaker or in the treatment of topics but also indirectly through the nature of the relationship between the company and the program provider (ie, if the provider believed that future financial support depended on producing programs that promoted the company's products).

Based on a draft policy statement, representatives of all State Affiliates of the American Association for Respiratory Care (AARC) were alerted to changing requirements at the May 1992 Leadership Training Conference. In November 1992, the FDA published revised guidelines for industry-sponsored scientific and educational activities.[3] At the May 1993 Leadership Training Conference, the specific directives from those guidelines were spelled out for attendees. In an effort to further help Affiliates fulfill their obligation to comply as they planned their statewide and regional meetings, two disclosure forms were mailed to presidents of State Affiliates and to members of the AARC House of Delegates. Completed forms must accompany each application for CRCE accreditation of a program that is submitted to the AARC. (Sample forms appear on Pages 1343-1345 of this issue of the Journal.)

Full disclosure is key to the entire process. Written records of the agreement between the company and the provider and between the speaker and the provider are essential. The written agreement should reflect that both the company and the provider agree that the activity is to be educational and nonpromotional and that the company has not dictated the design, conduct, or content of the program in a way that might bias the treatment of the topic. Speakers should also disclose their employment, stockholdings, consulting contracts, and amounts of research grant monies received from any manufacturer of commercial products discussed during the course of the presentation. Finally, the provider must disclose all such information to attendees at the educational activity.

Even before the FDA published these guidelines, the AARC maintained an 'arms-length' relationship with manufacturers. Attendees at the Annual Convention and Exhibition have probably noted that certain presentations are sponsored by equipment manufacturers or pharmaceutical firms. That sponsorship is clearly noted in the program supplied to all participants. What is not so apparent but has always been the policy of the Association is that speakers are suggested by the various Specialty Sections and Committees and ultimately approved

by the Program Committee, with no input from the sponsor. It is only in this fashion that attendees can be provided top quality educational opportunities—not promotions for products. Further, the educational grants that finance RESPIRATORY CARE Journal Conferences are acknowledged on the introductory pages of each Special Issue, but the grants are "no strings" grants, and the grantor cannot influence content. In a similar vein, the financial liaisons of authors are described in the title page footnote of each published paper.

The FDA recognizes the role of accrediting agencies in ensuring that industry-sponsored educational activities are independent and nonpromotional. So it is that the AARC is concerned with compliance. The intent is not to curtail industry sponsorship of continuing education but rather to assure that participants are not subjected to a biased presentation of data by a person who is no more than a shill for that company's product. It is a sort of 'truth in advertising' requirement. It is a matter of ethics.

Robert Czachowski PhD
Director of Education
American Association for Respiratory Care
Dallas, Texas

REFERENCES

1. Pushing drugs to doctors. Consumer Reports 1992;57(2): 87-94.
2. Cutaia JH. 1992 will be easy to swallow: drugmakers should see profits jump and the FDA become a lot more efficient. Business Week Jan 13, 1992:102.
3. Food and Drug Administration. Guidelines for sponsors of continuing education activities. Federal Register 1992;57(229), Friday Nov 27, 1992.

DISCLOSURE OF RELATIONSHIPS WITH COMMERCIAL ORGANIZATIONS FOR FACULTY PARTICIPATING IN CONTINUING EDUCATION PROGRAMS

Please see reverse side for policies and procedures.

NAME:

PROGRAM:

DATE(s) OF PROGRAM:

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I do not have any financial arrangements or affiliations with any of the commercial organizations offering financial support for this program, nor do I have any financial interest or other relationship with the manufacturer(s) of any commercial product(s) discussed in the educational presentation.

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Please return this form as soon as possible to the program chairman (name and address).

DISCLOSURE OF RELATIONSHIPS BETWEEN CE FACULTY AND COMMERCIAL COMPANIES

Policy

This program must be accredited by the Continuing Respiratory Care Education (CRCE) program of the AARC. AARC has adopted the following standard relating to disclosure by CE faculty:

a. Disclosure Policy for all CE Activities. A sponsor shall have a policy requiring disclosure of the existence of any significant financial interest or other relationship a faculty member or the sponsor has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. All approved CE activities shall conform to this policy.

b. Disclosure in Conference Materials. CE faculty or sponsor relationships with commercial supporters shall be disclosed to participants prior to educational activities in brief statements in conference materials such as brochures, syllabi, exhibits, poster sessions, and also in post-meeting publications.

The Education Department of the AARC requires the disclosure called for in the standards. A potential conflict of interest may be considered to exist if a faculty member is affiliated with or has a financial interest in organizations that may have a direct interest in the subject matter of a CE program in which he/she is participating. The intent of this policy is not to prevent a speaker with a potential conflict from making a presentation. Rather, it is intended to identify any potential conflict openly so that the listeners may form their own judgments about the presentation with full knowledge of the facts.

Procedures

1. A disclosure form will be filled out by all faculty participants.
2. The program chairman will be responsible for obtaining all the necessary disclosure forms from participants.
3. The prospective audience must be made aware of the affiliation/financial interest by an acknowledgement in the program or syllabus in the faculty listing.

For example:

John Doe, M.D.
Professor, Department of Medicine
ACME School of Medicine
Research Consultant, AJAX Pharmaceuticals
Madison, Wisconsin

or if Dr. Doe has a financial interest:

John Doe, M.D.
Professor, Department of Medicine
ACME School of Medicine
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The above named company agrees to make an educational grant in the amount of $_____ to support the following continuing respiratory care education program:

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This educational grant is given with the understanding that the program is for scientific or educational purposes and not for the purpose of promoting any product.

The Provider (i.e., your State Society) agrees to the following:

1. The State Society retains and is responsible for exercising full control over the planning of the program's content, including the selection of presenters and moderators.
2. The Provider agrees to ensure meaningful disclosure at the time of the program to the audience of (a) the Company's funding of the activity and (b) the relationships between the Provider and the Company and between the individual presenters or moderators and the Company.
3. The Provider agrees that there will be no advertisements for the Company's products in any materials disseminated in the program room.
4. The Provider agrees that when a product marketed by the Company or in competition with such a product is to be the subject of substantial discussion, the Provider will take steps to ensure that the data will be objectively selected and presented, that both favorable and unfavorable information about the product will be fairly represented, and that there is a balanced discussion of the prevailing body of scientific information on the product and of alternative treatment options.
5. The Provider agrees that there will be meaningful disclosure of any limitations on information that is presented. Such limitations or uncertainty include, but are not limited to, data that represent ongoing research, interim analysis, preliminary data, or unsupported opinion.
6. The Provider agrees that, in the case of live presentation, meaningful opportunity for scientific debate or questioning should be provided during the program.
7. The Provider will provide accreditation for the program in a manner consistent with the "Standards for Commercial Support of Continuing Respiratory Care Education" (the "Standards") of the AARC.
8. The Provider agrees to furnish the Company, on request, a report concerning the expenditure of the funds provided.

The Company agrees to the following:

1. The Company agrees not to direct or influence the content of the program and to play no role in the selection of presenters or moderators other that responding to Provider requests for suggestions of presenters or sources of possible presenters. If the Company responds to such a request, the Company agrees (a) to confirm its response in writing, (b) to provide, where reasonably possible, the names of more than one suggested presenter, (c) to provide a description of each suggested presenter's qualifications, (d) to disclose all known financial and other relationships between the Company and suggested presenter.
2. The Company agrees not to engage in scripting, targeting of points for emphasis or other activities that are designed to influence the content of the program.
3. The Company agrees not to have any promotional activities, such as presentations by sales representatives or promotional exhibits, in the same room as the educational activity.
4. The Company will otherwise abide by the Standards as they relate to commercial sponsors of continuing respiratory care education.
5. The Company agrees that all funding being provided for this program is included in this grant to the *State Society* and that no additional funding is being provided outside of this agreement.

On behalf of the Company:

Name	Signature	Date

On behalf of the Provider:

Ima Pro, RRT President, Your State Society	Signature	Date
Program Chairman	Signature	Date

Acute Pathophysiology after Wood Smoke Inhalation in a Dog Model: Effects of PEEP on Oxygenation and Lung Water

William R Clark MD, Gary F Nieman BS, and Tawfic S Hakim PhD

BACKGROUND: Wood smoke inhalation (WSI) inhibits pulmonary surfactant function within minutes of exposure, leading to atelectasis, venous admixture, hypoxemia, and pulmonary edema. We hypothesized that addition of positive end-expiratory pressure (PEEP), following WSI, would reinflate the lung and restore oxygenation. The possibility that PEEP may also affect pulmonary edema formation following WSI was also studied. METHODS & MATERIALS: Anesthetized dogs were ventilated with room air and instrumented for blood gas measurements and hemodynamic monitoring. After baseline data were collected, the animals were ventilated with wood smoke for 5 minutes and placed on either 5 or 10 cm H_2O PEEP [0.49 or 0.98 kPa], and studied for up to 4 hours. RESULTS: Smoke inhalation resulted in gross atelectasis, a decrease in arterial blood P_{O_2} (from 93 to 48 torr [from 12.4 to 6.4 kPa]), an increase in venous admixture from a mean (SD) of 8 (1) % to 40 (5) % and a decrease in pulmonary compliance (70% of baseline). When 5 cm H_2O PEEP [0.49 kPa] was used, these changes persisted for the duration of the experiment (4 hours). Addition of 10 cm H_2O PEEP [0.98 kPa] eliminated atelectasis and restored P_{aO_2} (95 torr [12.4 kPa]), venous admixture (5 [2] %), and compliance (95% of baseline) to near-normal values. At 2 hours following WSI, lung water increased but did not increase further over the next 2 hours regardless of PEEP level. CONCLUSIONS: In a canine model of wood smoke inhalation, lung collapse occurs immediately, resulting in hypoxemia. PEEP reinflates the lung and restores oxygenation but does not alter the amount or time course of lung water accumulation. [Respir Care 1993;38(12):1346-1354.]

Background

The pathophysiology of smoke inhalation has been extensively studied using the sheep,[1-15] dog,[16-22] goat,[23] rabbit,[24,25] and rat[26,27] as models. The Herndon-Traber laboratory (the most prolific contributor to smoke inhalation research) uses a sheep model and cotton as the fuel source for smoke.[1-9,13-15] Their studies suggest that much of the pulmonary damage caused by cotton smoke is secondary to leukocyte sequestration within the lung followed by release of toxic oxygen radicals and proteases.[4,6,9] Thus, the time course of the injury is delayed, with pathologic changes observed hours following smoke exposure.[1,6,7,14] Also, they found that cotton smoke does not alter surfactant composition[3] and that pulmonary edema does not develop for 32 hours following smoke exposure.[14] These findings are contradictory to those obtained from our studies,[18] even though the carboxyhemoglobin (COHb) levels, indicative of inhalation severity, were similar in both models.

Our laboratory uses a dog model and plywood sawdust as a fuel source. Others have also studied smoke inhalation using the dog model.[16-22] We chose to use plywood as a fuel source because it is a

Dr Clark is Professor of Surgery and Burn Service Director, Mr Nieman is Research Scientist, and Dr Hakim is Laboratory Director, Department of Surgery, State University of New York, Health Science Center at Syracuse New York.

Reprints: Gary F Nieman BS, Department of Surgery, SUNY Health Science Center, 750 East Adams Street, Syracuse NY 13210.

major constituent of many homes. This model simulates severe smoke inhalation as it might be encountered in the clinical setting and that would require intubation and ventilation.

Wood smoke inhalation, unlike cotton smoke inhalation, has an immediate pathologic effect on the lung. Lung compliance decreases and dense nonsegmental atelectasis quickly develops leading to increased venous admixture and hypoxemia.[16,18,20] Atelectasis secondary to wood smoke exposure is believed to be due to surfactant inhibition.[28] We have also demonstrated that a high-permeability pulmonary edema develops within 30 minutes of wood smoke exposure.[19,20]

The cited studies suggest that wood smoke inhalation may cause immediate lung injury. Therefore, we asked the question, "What is the initial pulmonary pathology following wood smoke inhalation and does increasing positive end-expiratory pressure (PEEP) have an effect on this pathology?" We hypothesized that if wood smoke does inhibit surfactant and cause atelectasis, then the addition of PEEP would reinflate the lung, reduce venous admixture, and restore adequate oxygenation.

Pulmonary edema plays a major role in smoke inhalation pathophysiology and occurs following both wood[18-20] and cotton[1,2,8] smoke inhalation. Therefore, we wanted to see if the addition of PEEP altered the time-course or magnitude of edema accumulation.

This study was designed to investigate the pathophysiology immediately following a controlled inhalation injury (standard smoke source and duration of exposure without the variables introduced by a concomitant thermal burn) and to analyze the effect of PEEP on these pathologic changes. This study does not address the use of PEEP as a possible ventilatory mode for prolonged use in the treatment of human victims of smoke inhalation. Also, this study emphasizes the likelihood that wood smoke, unlike cotton smoke, directly injures the lung and that pathologic changes begin immediately following exposure.

Methods and Materials

Mongrel dogs (n = 40) of both genders weighing between 15 and 20 kg (mean [SD] 18.6 [1.2] kg) were anesthetized initially with 25-30 mg sodium pentobarbital/kg body weight I.V.,[29] intubated with a 9- to 11-mm-ID cuffed endotracheal tube, and ventilated with room air using a Harvard ventilator.* An occlusive cuff seal was verified by observing a stable plateau pressure at peak inspiration. The dog model was chosen because our laboratory has years of experience with the dog model and an extensive database of hemodynamic, blood chemistry, and surfactant data generated from numerous acute-lung-injury studies in dogs. Supplemental doses of pentobarbital (3-5 mg/kg) were given as needed based on skeletal reflexes and blood pressure.[30] The initial tidal volume was set at 15 mL/kg and the respiratory rate at 15/minute. A femoral artery and vein were cannulated with 2-mm-ID polyethylene tubing using a cutdown technique. A 7-Fr flow-directed thermodilution catheter was placed in the pulmonary artery through an external jugular vein to measure pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP), and to determine cardiac output (C.O.) by thermal dilution. Cardiac index (CI) was then calculated:[31]

$$CI = \frac{C.O.}{BSA},$$

where BSA = body surface area calculated as
BSA = (0.112) (weight in kg).

The pressures were measured using disposable pressure transducers and were recorded on a chart recorder. The transducers were calibrated with a mercury column and positioned at heart level. When the chest was opened (left thoracotomy), we used a direct puncture of the myocardium to place a catheter in the left atrium to monitor left atrial pressure (LAP). Blood gases were measured with a blood gas analyzer that was calibrated using standardized controls and gas mixtures. Arterial blood was drawn and base deficit, when present, was corrected with sodium bicarbonate (1,000 mEq/L) using the equation:[32]

$$HCO_3^- \text{ (mL)} = \text{(base deficit) (weight in kg) (0.3)}.$$

All animals required this correction but only during the initial baseline period. Carboxyhemoglobin (COHb) determinations were made on arterial blood

*Suppliers are identified in the Product Sources section at the end of the text.

using a hemoximeter. Venous admixture ($\dot{Q}_s/\dot{Q}_t$) was calculated using the formula of Comroe et al:[33]

$$\frac{\dot{Q}_s}{\dot{Q}_t} = \frac{C_{aO_2} - C_{c'O_2}}{C_{c'O_2} - C_{\bar{v}O_2}},$$

where C_{aO_2} = arterial oxygen content; $C_{c'O_2}$ = capillary oxygen content; and $C_{\bar{v}O_2}$ = mixed venous oxygen content.

Mixed venous blood gas samples were taken from the pulmonary artery. Airway pressure was measured from a side port in the ventilator circuit 2 cm from the endotracheal tube connection. Static lung compliance (C_L) was calculated from data obtained by disconnecting the ventilator at end expiration and injecting a volume of air equal to twice the tidal volume into the lungs with a Collins 1-L syringe and noting the airway-pressure change caused by the injection.[33]

A PEEP of 5 cm H_2O [0.49 kPa] was added to prevent the loss of lung volume (a consequence of ambient pleural pressure) that resulted from opening the thorax, and to provide stability in inflation pressure, lung compliance, venous admixture, extravascular lung water (EVLW), and PAP for the duration of the experiment.[16,34] After a stabilization interval lasting 10-15 minutes, baseline data were collected. Animals were assigned to one of the three groups described in Table 1. Assignment was based on the final digit of a number provided by a random-number generator.

Table 1. Brief Description of the Protocol for each Experimental Group

Group	Protocol
Control	No smoke inhalation (n = 6)—maintained on 5 cm H_2O PEEP.
Smoke + 5 cm H_2O PEEP	Wood smoke inhalation (5 min)—maintained on 5 cm H_2O PEEP. Animals killed at 2 h (n = 10) and 4 h (n = 8) after smoke inhalation for EVLW measurement. Data combined (n = 18) at baseline, 5, 60, and 120 min after smoke inhalation.
Smoke + 10 cm H_2O PEEP	Wood smoke inhalation (5 min)—maintained on 10 cm H_2O PEEP. Animals killed at 2 h (n = 10) and 4 h (n = 6) post smoke for EVLW measurement. Data combined (n = 16) at baseline, 5, 60, and 120 min after smoke inhalation.

Smoke was generated by burning an aliquot of a standard mixture of fir-plywood sawdust and kerosene.[16] After ignition, the combustion chamber was placed in the inspiratory line of the ventilator circuit so that smoke reached the airway at a temperature of 37°C. The experimental setup is shown in Figure 1. Smoke was delivered for 5 minutes of uninterrupted tidal respiration, and then ventilation with room air was re-established. Data acquisition was repeated at 5, 60, 120, 180, and 240 minutes following smoke (or air for the controls) exposure. At the end of the experiment, the animal was killed with an infusion of sodium pentobarbital (6 gr/10 lb body weight) given via the peripheral vein.[35] The lungs were removed immediately en bloc. An assay for EVLW (mL H_2O/g blood-free dry lung) was done using the method of Pearce et al, which compensates for blood retained in the lung.[36] Data are expressed as mean (standard deviation). Statistical significance was determined using a one-way analysis of variance (ANOVA). Significance between mean values within the same group was determined with a second ANOVA. If the F ratio indicated the presence of significant differences, a Tukey's test was used to identify these differences. A p value of < 0.05 was required for comparisons to attain statistical significance.

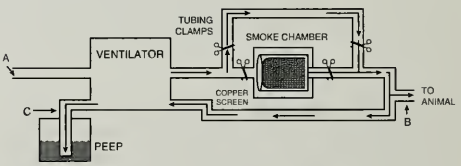

Fig. 1. Schematic of the experimental apparatus. Room air enters the ventilator at 'A' and is selectively channeled through the smoke chamber or diverted around it. Tubing clamps, applied to the smoke channel, allow the animal to breathe room air. In like manner, the animal breathes smoke when the room-air channel is closed and the smoke channel is open. Airway pressure is measured at 'B'; exhaled gas passes through a calibrated water chamber and PEEP results (C).

Results

Figure 2 shows the results of the five major outcome variables we measured. Visual observation of the lung (recall that the chest was open) demonstrated that smoke exposure immediately caused atelec-

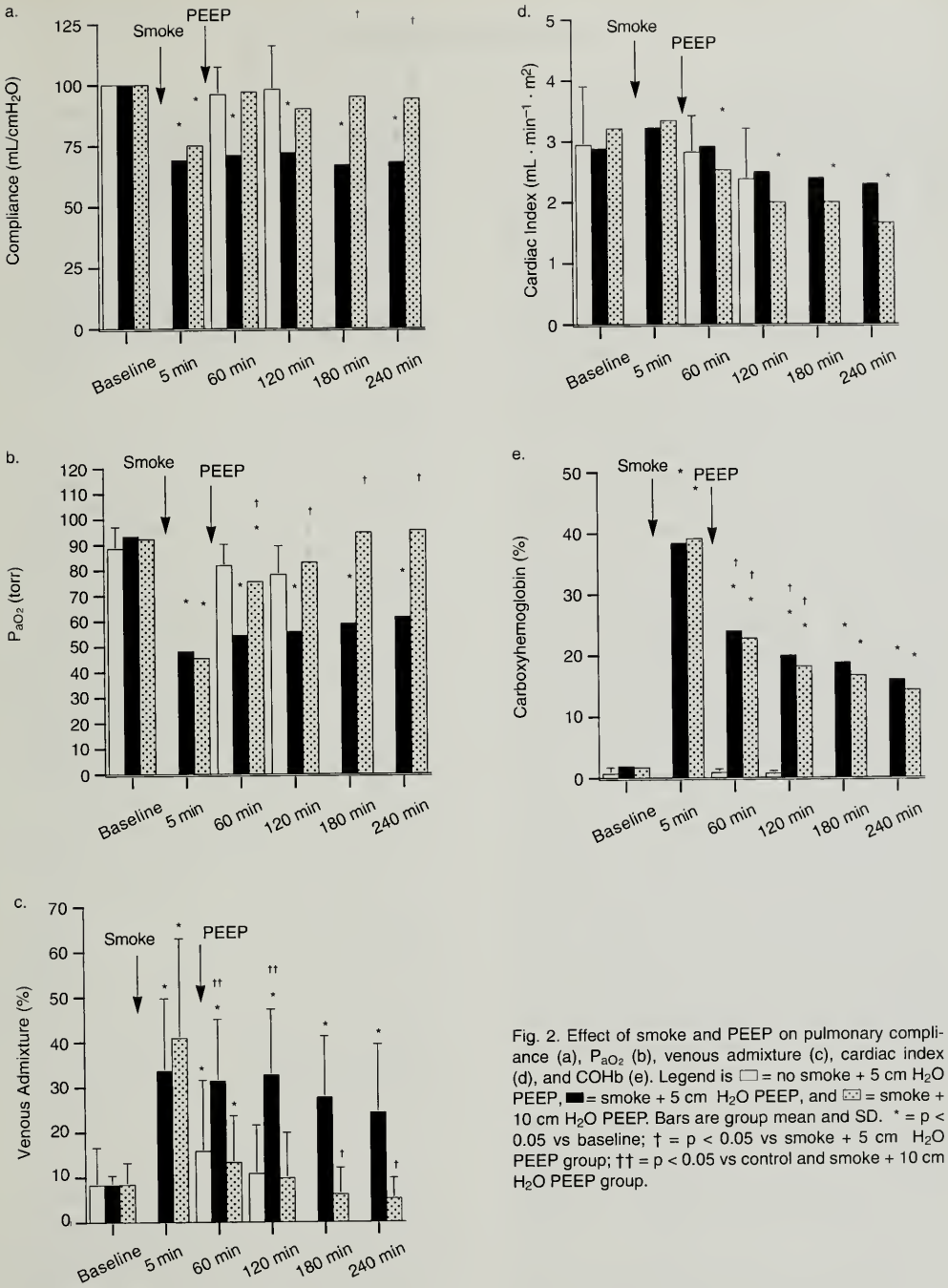

Fig. 2. Effect of smoke and PEEP on pulmonary compliance (a), P_{aO_2} (b), venous admixture (c), cardiac index (d), and COHb (e). Legend is □ = no smoke + 5 cm H_2O PEEP, ■ = smoke + 5 cm H_2O PEEP, and ▩ = smoke + 10 cm H_2O PEEP. Bars are group mean and SD. * = $p < 0.05$ vs baseline; † = $p < 0.05$ vs smoke + 5 cm H_2O PEEP group; †† = $p < 0.05$ vs control and smoke + 10 cm H_2O PEEP group.

tasis and a general decrease in lung volume. This observation was corroborated by a decrease in pulmonary compliance (Fig. 2a) in both smoke-exposed groups 5 minutes after smoke inhalation. The atelectasis resulted in a fall in arterial P_{O_2} (Fig. 2b) and increased venous admixture (Fig. 2c) 5 minutes following smoke inhalation. Cardiac index (Fig. 2d) did not change 5 minutes after smoke inhalation. Smoke exposure was uniform in both smoke groups as evidenced by similar levels of COHb (Fig. 2e). Also, none of the physiologic data were significantly different between smoke-exposed groups (5 minutes after smoke inhalation before addition of 10 cm H_2O PEEP [0.98 kPa]), indicating a similar level of injury to both smoke-inhalation groups.

Addition of 10 cm H_2O PEEP [0.98 kPa] visibly reduced the amount of atelectasis and increased lung volume. Increasing PEEP to 10 cm H_2O [0.98 kPa] returned pulmonary compliance to near baseline values; whereas with 5 cm H_2O PEEP [0.49 kPa], compliance remained significantly below baseline values for the duration of the experiment (4 hours, Fig. 2a). When animals were maintained on 5 cm H_2O PEEP [0.49 kPa], P_{aO_2} (Fig. 2b) and venous admixture (Fig. 2c) remained statistically significantly different from baseline values throughout the experiment. Increasing PEEP to 10 cm H_2O [0.98 kPa] returned venous admixture and P_{aO_2} to near baseline values 2 hours following smoke inhalation. CI did not significantly change from baseline with the addition of 5 cm H_2O PEEP [0.49 kPa], but did fall below baseline with addition of 10 cm H_2O PEEP [0.98 kPa] (Fig. 2d). However, CI was not statistically significantly different between groups at any time period. Systemic blood pressure fell 1 h following smoke exposure in both PEEP groups but returned to near-baseline values by 4 h. Blood pressure did not change from baseline in the control animals. These data are presented in Table 2. Pulmonary artery pressure was significantly increased 5 minutes after smoke inhalation but returned to near-baseline by 1 h. These data, baseline and 5 min after smoke inhalation, are shown in Table 3. There was no change from baseline in pulmonary artery pressure for controls. We saw no significant change in PCWP in the Control or Smoke + 5 groups. Smoke did not change PCWP in the Smoke + 10 group, but the addition of PEEP did increase PCWP. Mean (SD) at baseline = 6.0 (1.1) and with 10 cm H_2O PEEP, 8.9 (2.0) ($p < 0.05$). Smoke inhalation resulted in elevated lung water at both 2 and 4 hours following exposure, but neither the time after smoke inhalation (2 or 4 hrs) nor the level of PEEP (5 or 10 cm H_2O [0.49 or 0.98 kPa]) significantly altered EVLW (Table 4). Although all of the measurements of extravascular lung water following smoke inhalation were significantly greater than those of the controls, they were not different from each other.

Table 2. Changes in Mean Systemic Blood Pressure in Smoke-Exposed Dogs

PEEP (cm H_2O)	Time after Exposure		
	Baseline (torr)	1 Hour (torr)	4 Hours (torr)
5	121.7 (16.8)*	91.4 (15.9)†	101.9 (32.0)
10	107.2 (16.8)	76.9 (16.5)†	95.8 (18.8)

*Values are mean (SD).
†Compared to baseline and 4 hours after smoke exposure, $p < 0.005$.

Table 3. Pulmonary Artery Pressure at Baseline and after 5 Min of Smoke Inhalation

PEEP (cm H_2O)	Time after Exposure	
	Baseline (torr)	5 Min (torr)
5	14.8 (2.8)*	19.8 (3.6)†
10	14.4 (2.4)	19.1 (4.1)†

*Values are mean (SD).
†Compared to baseline measurement, $p < 0.05$.

Table 4. Changes in Mean Extravascular Lung Water (EVLW) in Smoke-Exposed Dogs*

PEEP (cm H_2O)	Time after Exposure	
	2 Hours (mL/g)†	4 Hours (mL/g)
5	6.09 (2.40)	4.73 (0.77)
10	5.3 (0.85)	5.11 (1.10)

*Values are mean (SD); EVLW in control animals = 3.84 (0.14); $p < 0.005$ for control vs all measurements after exposure.
†Units are mL H_2O/g dry lung.

Discussion

The results of the present study are consistent with previous studies using a canine model of smoke inhalation.[16,18,19,37] The response to wood smoke exposure was qualitatively similar in all animals; it included atelectasis, decreased compliance,

increased venous admixture, and edema. Atelectasis is believed to be due to pulmonary surfactant inhibition by wood smoke.[16,18,28] It is important to note that wood smoke inhalation causes immediate pulmonary injury in contrast to cotton smoke inhalation, which causes a delayed lung injury.[1,6,7,14] These data are significant because they demonstrate that pulmonary pathology, in smoke-inhalation patients, may be present immediately upon hospital admission but take several hours to become clinically obvious.

Our results show that 10 cm H_2O PEEP eliminated gross atelectasis, reduced venous admixture, returned blood gases to normal, and restored C_L to near-baseline values following acute smoke inhalation. Increasing PEEP did not alter the time-course of COHb reduction. This suggests that alveolar ventilation is not the primary regulator of COHb. Wood smoke inhalation also resulted in pulmonary edema, which was evident as early as 2 hours following exposure and was not influenced by the level of PEEP.

PEEP is recognized as a potential modifier of EVLW in two possible ways. (1) PEEP may alter the Starling forces, which govern fluid filtration in the capillaries. The relationship between the hydrostatic and oncotic forces within pulmonary capillaries and those in the interstitial space surrounding the capillaries governs fluid movement out of the vessels.[38] EH Starling[39] defined this relationship as the difference in the hydrostatic pressures minus the difference in the oncotic pressures. It is possible that PEEP increases interstitial hydrostatic pressure and thus decreases fluid flux. (2) PEEP may alter the interstitial capacity to store fluid, thus redistributing the existing lung water in the extravascular space of the lung—edema cuffing. The interstitial space surrounding pulmonary vessels acts as an emergency reservoir for edema fluid as it moves out of the pulmonary capillaries. The perivascular space expands as it becomes fluid filled, creating cuffs completely surrounding the vessels.[20] Alveolar flooding does not take place until these cuffs are completely saturated. This study showed no improvement in EVLW as a result of ventilation and 10 cm H_2O PEEP. In other studies,[40,41] the investigators found that the use of PEEP increased the perivascular fluid cuffs (the ability of the vessel wall to store fluid) in the lung without affecting total lung water. Although we did not quantify the size of the perivascular cuffs, it is possible that PEEP may have redistributed EVLW from the interstitium into the larger perivascular space. According to these reports, this effect of PEEP improves gas exchange. Also, it is interesting that, in our study, EVLW did not increase with time in a predictable, stepwise manner. We found no difference in EVLW between 2 and 4 hours after smoke exposure in either PEEP group. This suggests that wood smoke causes a rapid increase in EVLW that is maintained for at least 4 hours after smoke-inhalation injury.

In addition to its effect on the Starling forces, PEEP may have influenced the zone conditions in the lungs.[42] For example, in the open-chest animals with 5 cm H_2O PEEP [0.49 kPa], the lung was mostly under zone 3 conditions (perfusion constant); whereas with 10 cm H_2O PEEP [0.98 kPa], the lungs would be under zone 2 conditions (perfusion cyclic, varying inversely with alveolar pressure changes) throughout the respiratory cycle.[42] Thus, in addition to the effects on interstitial hydrostatic pressure, it is possible that changes in zone conditions could have altered the course of edema.[34,43] However, the net effect was small, and it is possible that besides the redistribution of existing EVLW, the change in hydrostatic force caused by PEEP may have diminished filtration in some alveolar vessels while enhancing filtration in extra-alveolar vessels.[44]

It is worth emphasizing that the lack of significant change in EVLW with PEEP is not unique to smoke inhalation injury. In oleic acid injury[41] and high-pressure edema,[42] PEEP did not change the total EVLW. However, with surface-tension-induced pulmonary edema,[45] PEEP increased the total EVLW, and simultaneously improved gas exchange.

Another common hemodynamic consequence of PEEP is a reduction in C.O.[46,47] This potentially deleterious effect can be overcome by fluid administration and the use of inotropic agents.[48] This implies, of course, that fluid infusion is safe in clinical situations in which resuscitation is mandatory and in which the effects of PEEP on systemic hemodynamics are appreciated and compensated for. PEEP restores venous admixture toward baseline levels by reinflating collapsed alveoli.[49,50] The increase in dead-space ventilation following the institution of PEEP[49,50] is the result of a pressure-related reduction in alveolar capillary perfusion that can be com-

pensated for by increasing the vascular pressure pharmacologically or with fluid administration. Consequently, more lung units shift back to zone 2 or zone 3 conditions.[42]

The use of PEEP with the smoke-damaged lung is somewhat controversial in that PEEP may result in overdistention of patent alveoli rather than the recruitment of collapsed alveoli.[50-52] This overdistention results ultimately in diversion of blood flow to the collapsed alveoli and an increase in venous admixture. In one study, cotton smoke inhalation in intact sheep increased dead-space ventilation but did not improve ventilation-perfusion matching.[51] The cause for this discrepancy in results is not clear and may be related to model (dog vs sheep) or smoke type (wood vs cotton) differences. In contrast, in the present study, PEEP decreased venous admixture, suggesting improved ventilation-perfusion matching. Because wood smoke inhalation results in atelectasis, secondary to surfactant deactivation,[16] PEEP probably improves ventilation-perfusion matching by recruitment of collapsed alveoli.

This study does not address the efficacy of the prophylactic use of PEEP in patients with smoke-inhalation injury—that is PEEP used before incontrovertible respiratory failure is established.[53] Clinical studies on the prophylactic use of PEEP provide empirical evidence that is unreliable because of imprecise diagnostic criteria for respiratory failure and because of patient heterogeneity. For the most part, these studies support the use of prophylactic PEEP as a way of modifying the severity of the respiratory failure that develops and of shortening the duration of ventilatory support.[48,53] Prophylactic PEEP makes good theoretical sense because, in our experience, alveolar function is easier to maintain than to restore after dense atelectasis has occurred. Several clinical studies support the efficacy of PEEP following smoke-inhalation injury.[53,54]

Smoke inhalation is characterized by diagnostic uncertainty, the insidious onset of respiratory failure, and the frequent respiratory complications arising from the skin burn present in over 75% of inhalation-injury patients.[55] The course of the burn illness often includes septic complications that are unaffected by PEEP.[54] The importance of these sequential stresses on the smoke-injured lung is the observation that, in patients with smoke inhalation but no skin burn, the mortality and morbidity is much lower than it is in patients with both smoke inhalation and skin burn.[55-57] There is no evidence that PEEP offers any advantage to the healing process in injured or damaged lungs.[58] However, it seems intuitively correct to conclude that use of PEEP would enhance recovery if it could improve lung function and maintain alveolar patency following smoke inhalation.

Conclusions

This study demonstrates that wood smoke causes instantaneous lung injury (ie, atelectasis, decreased pulmonary compliance, and increased shunt and pulmonary edema) probably due to pulmonary surfactant inhibition. Application of adequate levels of PEEP reinflates the lung, improving gas exchange, reducing venous admixture, and increasing lung compliance of smoke-damaged lungs. However, increasing PEEP does not alter the magnitude or time-course of pulmonary edema accumulation.

PRODUCT SOURCES

Animal ventilator (Model 613), Harvard Apparatus Corp, South Natick MA

Cardiac Output Computer (Model 9525), American Edwards Laboratories, Irvine CA

Sorenson Transpac II disposable pressure transducer, Abbott Laboratories, North Chicago IL

Carrier amplifier (Model 8805B) and 4-channel recorder (Model 954B-100), Hewlitt Packard Co, Waltham MA

Acid Base Laboratory (Model ABL2), Radiometer America Inc, Westlake OH

Hemoximeter (Model OSM2), Radiometer America Inc, Westlake OH

Instat Statistical Software v 2, GraphPad Software Inc, San Diego CA

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Factors Affecting Microbial Colonization of the Trachea and Septicemia in Mechanically Ventilated Neonates

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BACKGROUND: The influence of pulmonary surfactant administration, long-term dexamethasone therapy, and presence of central venous catheters (CVCs) on microbial colonization of the trachea and neonatal septicemia is largely unknown. We examined these relationships using a case-control design. MATERIALS & METHODS: We retrieved data from the medical record and reviewed tracheal aspirate (TA) and blood (BL) cultures from 251 infants born at University Hospital. These infants, who were intubated for an average of 21 days, provided 607 TA (52% positive) and 470 BL (10% positive) cultures. Surfactant (Exosurf) was given to 158 patients; of these, 42 were matched by birthweight, race, and gender to 42 non-treated patients. Thirty-three of 67 dexamethasone-treated infants and 28 of 44 patients requiring CVCs were also similarly matched to controls. RESULTS: Tracheal colonization increased from 26% at 1 week to 94% at 4 weeks. Gram-negative flora increased from 10% of the first week's positive cultures to 30% of the fifth week's positive cultures, then declined. Yeast decreased from 10% of the first week's positive cultures to 5% of the positive cultures taken at 4 weeks. TA Gram-positive flora remained unchanged in composition throughout the period of observation—*Staphylococcus epidermidis* 34%, *Staphylococcus haemolyticus* 17%, *Streptococcus* species 13%, *Staphylococcus aureus* 5%, and mixed organisms 30%. In 36 patients, BL and TA samples, taken within 48 hours of each other, grew the same organism 13 times. Percent positive TA and BL cultures, types of pathogens, and pattern of tracheal colonization were similar for all study groups. Positive BL cultures occurred in 34% of the 44 patients with CVCs and in 9% of the remaining 207 infants. CONCLUSIONS: Neither surfactant nor dexamethasone alter tracheal colonization patterns nor increase the incidence of neonatal septicemia. Central venous catheterization does not alter tracheal colonization but along with birthweight and gestational age poses significant risk for neonatal septicemia ($p = 0.004$ and 0.04, respectively). Weekly TA cultures detect the introduction of pathogens capable of causing nosocomial infection but, in this group of patients, were of limited value in predicting late-onset septicemia. [Respir Care 1993;38(12):1355-1363.]

Background

Routine cultures of tracheal aspirates (TA) from mechanically ventilated neonates have been valuable in the identification of the bacterial agents of congenital pneumonia,[1] whereas routine TA culture surveillance has not reliably predicted the bacterial pathogens likely to be isolated in late-onset septicemia.[2-4] Thus, the value of serial TA cultures has been limited to the characterization of tracheal flora.[5,6] However, most of the studies cited were conducted before the widespread use of exogenous pulmonary surfactant for prevention and/or treatment of hyaline membrane disease (HMD) and the use of corticosteroids for the treatment of bronchopulmonary dysplasia (BPD).[7-14] It has been proposed that the administration of surfactant and/or dexamethasone would not increase the risk of infection.[15] These studies, however, involved few infants

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and did not address the specific issue of bacterial colonization of the airways.[7-15]

The purpose of the present investigation was to describe the bacterial colonization of the trachea in mechanically ventilated newborns in a neonatal intensive care unit (NICU) and to relate colonization to the administration of exogenous pulmonary surfactant and systemic corticosteroids and to placement of central venous catheters (CVCs). The temporal relationship between airway bacterial colonization and culture-proven septicemia was also explored.

Materials and Methods

Two hundred and fifty-one infants born at University Hospital during 1991 and 1992 who were intubated longer than 1 day comprised the study population. All infants required mechanical ventilation; a neonatal pressure-limited time-cycled ventilator* was used. Three of these infants were temporarily treated with high-frequency ventilation because of pulmonary interstitial emphysema.

Blood cultures (BL), complete blood counts (CBC), and chest radiographs were performed on all infants upon admission to the NICU. Subsequent blood cultures were also taken whenever infections were suspected. All infants were treated prophylactically with ampicillin (100 mg · kg^{-1} · day^{-1} I.V. given in 2 doses q 12 h) and gentamicin (5 mg · kg^{-1} · day^{-1} I.V. given in 2 doses q 12 h). This regimen was continued for 3-5 days if the cultures were negative, 5-7 days if cultures were negative but clinical signs of infection were present, 7-10 days if cultures were positive, and 14-21 days if there were signs of meningitis. Infants who developed sepsis late in their hospital course were treated with gentamicin and vancomycin. Once isolates were identified, the antibiotic therapy was changed according to the results of microbial sensitivity studies.

Tracheal aspirates were obtained weekly under sterile conditions. First, 0.5 mL of normal saline was introduced into the endotracheal tube, then suction was applied and the specimen collected into a sealed container. Bacteriologic cultures were processed using standard laboratory procedures.[16] Antibiotic sensitivities were obtained for all bacterial isolates.

All infants required umbilical artery catheterization, and those who needed long-term intravenous therapy underwent CVC placement. For this procedure a cuffed silicone catheter was tunneled under the skin and terminated in a central vein.[17] In our NICU most catheters are inserted through the saphenous vein and placed in the inferior vena cava.

Exogenous synthetic surfactant (Exosurf) was given (5 mL/kg body weight given in 2 doses q 12 h) intratracheally. When indicated, infants were given dexamethasone sodium phosphate (0.5 mg · kg^{-1} · day^{-1} given in 2 doses q 12 h) intravenously for 3 days. Thereafter a 10% decrease in dosage every 3 days was initiated and continued for up to 4 weeks.[7,8]

Data Collection and Statistical Analysis

Our NICU is managed under a prospective plan of patient care, which did not change over the study period. Results of the bacteriologic cultures were collected concurrently and stored in the hospital laboratory computer system. Demographic and clinical information for the 251 infants was retrospectively obtained from the hospital medical records. Subgroups were formed for specific analyses. Forty-two patients who received exogenous surfactant were individually matched by birthweight to 42 infants who did not receive surfactant. On a group basis, gender and weight were comparable. Thirty-three infants who received dexamethasone were similarly matched to 33 who did not. Twenty-eight infants who underwent CVC placement were matched by birthweight, race, gender, length of hospitalization, and duration of intubation to 28 infants who did not. The results are reported as mean (SD). Paired *t* test was used to analyze the significance of the mean difference in birthweight.[18] Unpaired *t* tests were used to analyze the significance of the difference of group means of gestational age, duration of umbilical artery catheterization, duration of central venous catheterization, duration of intubation, and length of hospital stay. A χ^2 test on proportions was used for gender, race, premature rupture of membranes, positive blood cultures, and route of delivery.

*Suppliers are identified in the Product Sources section at the end of the text.

Every patient from the three matched groups described above was used in a multivariate analysis to assess combined treatment effects. Each of these 115 infants was classified as negative (no positive blood culture, n = 95) or positive (one or more positive blood cultures, n = 20). Forward stepwise logistic regression was employed to assess the influence of birthweight, gestational age, gender, umbilical artery catheterization, duration of intubation, length of hospital stay, surfactant administration, dexamethasone treatment, and placement of CVCs, on the incidence of positive blood cultures. Using only patients from the three matched groups increased the comparability of the sample for multivariate analysis more than if all 251 patients had been used.

Results

Of the 251 infants whose records were reviewed, 26% were intubated for less than 2 weeks, 34% between 2 and 3 weeks, and the remaining 40% were intubated longer than 3 weeks. Characteristics of the study population are presented in Table 1: 47 of the 251 infants were Black, 2 Oriental, 2 Hispanic, and the remaining were Caucasian; 224 were singletons; 50% were delivered by cesarean section. Etiology of the respiratory failure was HMD (70%), respiratory failure of nonpulmonary cause (20%), and meconium aspiration or pneumonitis (10%). Seventeen of the 251 infants (7%) died either during the neonatal period or during the first 6 months of life.

Tracheal Aspirate Cultures

We found 607 TA cultures from 217 patients who were intubated longer than one week. Of these, 392 were positive. The distribution of positive cultures is shown in Figure 1; each bar is a composite for that time period showing the percent of positive TA cultures that were Gram-positive, Gram-negative, and yeast. Tracheal colonization increased from 26% at 1 week to 94% at 4 weeks. Gram-negative flora increased from 10% of the first week's positive cultures to 30% of the fifth week's positive cultures, then declined. Yeast decreased from 10% of the first week's positive cultures to 5% of the positive cultures obtained at 4 weeks. TA Gram-positive flora remained unchanged in composition throughout the period of observation—*Staphylococcus epi-*

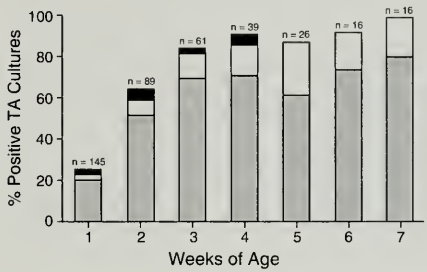

Fig. 1. Bacterial colonization of the trachea in 251 mechanically ventilated infants. ▨ = Gram-positive, □ = Gram-negative, and ■ = yeast.

Table 1. Population Studied To Determine Factors Affecting Tracheal Colonization and Septicemia

Birthweight (g)	Number of Patients	Number of Patients Dead	Gestational Age (weeks)	Duration of Intubation (days)	Length of Stay (days)
501-750	18	6	27 (2)*	39 (27)*	56 (35)*
751-1,000	51	7	27 (1)	30 (18)	57 (21)
1,001-1,250	44	1	28 (2)	20 (14)	45 (17)
1,251-1,500	44	2	30 (2)	11 (10)	35 (12)
1,501-1,750	25	0	31 (1)	9 (9)	29 (11)
1,751-2,000	18	0	33 (2)	12 (17)	26 (16)
≥ 2,001	51	1	35 (5)	16 (8)	17 (1)
Total	251	17	30 (4)	17 (17)	37 (23)

*Values are mean (SD).

dermidis 34%, *Staphylococcus haemolyticus* 17%, *Streptococcus* species 13%, *Staphylococcus aureus* 5%, and mixed organisms 30%.

Gram-negative flora was represented by *Serratia marcescens* (31%), *Escherichia coli* (22%), *Enterobacter cloacae* (18%), and mixed flora (29%). It should be noted that *S marcescens* was recovered from a cluster of 5 patients during a 2-month period only.

Septicemia and TA Cultures

Of the 251 patients included in this study, 34 developed one (26 patients) or more than one (8 patients) episode of bacteriologically proven septicemia during hospitalization. Of the 34 septic infants, 33 responded to treatment promptly and presented negative follow-up BL cultures. The exception was an infant from whom *Klebsiella pneumoniae* was cultured 3 times during 72 hours before responding to cefotaxime (150 $mg \cdot kg^{-1} \cdot day^{-1}$ I.V. given in 3 doses q 8 h). Three of the 34 infants who developed septicemia later died from complications unrelated to sepsis.

Seven of the 44 positive blood cultures were taken immediately after birth (3 Group B *Streptococcus* species, 2 *E coli, 1 Candida albicans,* and 1 *S marcescens).* Four positive blood cultures occurred during the first week of life, 21 others between the second and fourth weeks, and the remaining 12 cultures were obtained after the fourth week. Twenty-two of the 37 nosocomial infections were due to Gram-positive bacteria (14 *S epidermidis,* 8 *S haemolyticus),* 10 infections were due to Gram-negative bacilli (4 *K pneumoniae,* 1 *E Coli,* 2 *S marcescens,* 2 *E cloacae,* 1 *Salmonella* species), and *C albicans* accounted for the remaining 5 cases.

The relationship between TA and BL isolates was studied in 36 patients whose samples were taken either simultaneously or within 48 hours of each other. At the time of positive BL culture, 13 TA were negative, 10 TA were positive with a different organism, and 13 TA (36%) grew the same organism as in blood (6 *S epidermidis,* 2 *S haemolyticus,* 2 *E coli,* 1 *S marcescens,* 1 *E cloacae,* and 1 *C albicans).*

Organisms isolated from TA that were different from those obtained from blood included 1 *S aureus,* 1 *S haemolyticus,* 4 *S epidermidis,* 1 *S marcescens,* 2 *P aeruginosa,* and 1 yeast.

Exogenous Pulmonary Surfactant and TA Cultures

One hundred and fifty-eight (63%) of the 251 infants received two doses of exogenous surfactant

Table 2. Comparison of Variables in 42 Surfactant-Treated Infants and 42 Controls

	Treatment mean (SD)	Control mean (SD)	p Value
Birthweight (grams)	1,323 (609)	1,333 (693)	0.46*
Gestational age (weeks)	29 (3)	30 (4)	0.52†
Race (Caucasian/Black)	36/6	33/9	0.56‡
Gender (male/female)	28/14	27/15	1.00‡
Premature rupture of membranes (patients)	22	24	0.83‡
Cesarean deliveries	18	22	0.65‡
Umbilical arterial catheter (days)	12 (7)	9 (5)	0.04†
Central venous catheter (days)	32 (17)	22 (8)	0.05†
Duration of intubation (days)	27 (18)	19 (17)	0.02†
Duration of hospitalization (days)	48 (23)	36 (23)	0.04†
Positive blood cultures (patients)	5	7	0.52‡

*Paired *t* test.
†Unpaired *t* test.
‡χ^2.

after the first and before the 24th hour of life. Characteristics of 42 of these patients and their matched controls are presented in Table 2. As expected, birthweight, gestational age, gender, and racial distribution were similar among the groups. The occurrence of prolonged rupture of membranes (PROM) and cesarean delivery was also similar. Because exogenous surfactant was administered to neonates with severe HMD (patients whose $P_{aO_2}/P_{AO_2} < 0.22$), infants in the control group had a less complicated hospital course, clearly documented by the need of patients in the surfactant group to remain intubated longer (1,136 days vs 821 days) and also to require longer hospitalization (2,041 vs 1,539 days). Sicker infants required prolonged catheter placements (312 days for those treated and 164 days for those not treated with surfactant). During the study period, 103 blood cultures (13% positive) were taken from the 44 surfactant and 63 (10% positive) from the 44 nonsurfactant-treated infants. No differences were found in the species of organisms isolated from either group.

Due to the differences in duration of endotracheal intubation, more tracheal aspirates were taken from surfactant-treated infants (144) than from those who were not treated (96). For both groups the percentage of positive TA cultures was similar (53 and 59%, respectively). Tracheal aspirate colonization pattern was identical for surfactant-treated infants and controls. Acquisition of Gram-positive and Gram-negative bacteria and yeast was similar to that of the entire group (Fig. 1).

Dexamethasone Therapy and TA Cultures

Of the 251 infants, 67 (27%) received a prolonged course of corticosteroids for the treatment of BPD. Characteristics of 33 of these infants and their matched controls are presented in Table 3. It can be seen that both groups were similar not only in demographics but also in the incidence of PROM and mode of delivery. The number of infants who required umbilical artery catheterization and the duration of catheterization were comparable. Fifteen patients in the dexamethasone group needed CVCs for an average of 27 days, whereas the 11 patients in the control group required CVCs for an average of only 15 days. This difference was statistically significant ($p = 0.04$). The cases also required mechanical ventilation and hospitalization longer than controls. The number of TA and BL cultures taken was higher in the group of infants treated with corticosteroids. The percent of positive TA and BL cultures, however, was not statistically significantly different ($p = 0.2$).

Table 3. Comparison of Variables in 33 Dexamethasone-Treated Infants and 33 Controls

	Treatment mean (SD)	Control mean (SD)	p Value
Birthweight (grams)	932 (207)	922 (219)	0.38*
Gestational age (weeks)	27 (2)	27 (2)	0.25†
Race (Caucasian/Black)	29/4	30/3	0.67‡
Gender (male/female)	23/10	19/14	0.51‡
Premature rupture of membranes (patients)	16	15	1.00‡
Cesarean deliveries	15	14	1.00‡
Umbilical arterial catheter (days)	12 (10)	11 (6)	0.33*
Central venous catheter (days)	27 (15)	25 (14)	0.44†
Duration of intubation (days)	39 (18)	31 (13)	0.03†
Duration of hospitalization (days)	62 (17)	57 (20)	0.16†
Positive blood cultures (patients)	7	6	1.00‡

*Paired *t* test.
†Unpaired *t* test.
‡χ^2.

Dexamethasone treatment was started at approximately 3 weeks of life. TA bacterial colonization pattern before and after 3 weeks of life was not different between dexamethasone-treated and non-treated infants and was similar to that described for the entire study population. The number of yeast and Gram-positive and Gram-negative bacteria recovered from blood from both groups of infants was also similar.

Central Venous Catheter, TA, and Blood Cultures

Forty-four (17%) of the 251 infants included in this study underwent placement of a CVC for a total duration of 1,080 days (average of 24.5 days per patient). Fifteen of the 44 (34%) infants who underwent central venous catheterization and 19 of the 207 (9%) who did not, developed positive BL cultures sometime during the hospitalization. In order to assess the relationship between CVC placement, positive blood, and TA cultures, 28 infants who underwent the procedure were matched to 28 infants who did not (Table 4). Demographic characteristics, duration of endotracheal intubation, and length of hospitalization were similar. Infants with CVCs presented clinical signs of sepsis that required 105 BL cultures (15% were positive), whereas control infants required only 72 (13% were positive). Isolates from the CVC group included 8 Gram-positive cocci, 4 Gram-negative bacilli, and 4 yeast. Those obtained from the controls included 6 Gram-positive cocci and 3 Gram-negative bacilli. Some infants presented multiple positive blood cultures. Thus, 10 out of 28 CVC patients (36%) and 4 of the control infants (14%) developed culture-proven sepsis. This difference was statistically significant ($p = 0.02$). All infants recovered from their septic episodes. TA isolates were similar among all infants regardless of the presence of a CVC. Furthermore, the colonization pattern was almost identical to that described for the controls and the study population as a whole.

Results of the step-wise logistic regression analysis indicated that low birthweight and gestational age were strongly associated with septicemia ($p = 0.004$ and 0.04, respectively). However, after birthweight was entered into the regression, gestational age was no longer significant ($p > 0.05$). CVC placement was the next variable that added significantly to the risk ($p = 0.04$). Neither exogenous surfactant ($p = 0.29$) nor dexamethasone treatment ($p = 0.46$) was significantly associated with the incidence of neonatal septicemia.

Discussion

Mechanically ventilated newborns have been exposed to three separate environments that contribute to their pattern of microbial colonization: the uterus, the maternal vaginal tract (except in cases of cesarean delivery), and the microbial environment of the NICU. Tracheal aspirate cultures taken shortly after birth from infants who are septic or who suffer from congenital pneumonia can provide valuable baseline bacteriologic information.[1-5] Among these

Table 4. Comparison of Variables in 28 Central-Venous-Catheter-Treated Infants and 28 Controls

	Treated mean (SD)	Control mean (SD)	p Value
Birthweight (grams)	1,006 (280)	990 (265)	0.19*
Gestational age (weeks)	27 (2)	27 (2)	0.25†
Race (Caucasian/Black)	25/3	26/2	0.30‡
Gender (male/female)	13/15	14/14	0.29‡
Duration of intubation (days)	37 (1)	36 (1)	0.42†
Duration of hospitalization (days)	64 (9)	64 (10)	0.44†
Positive blood cultures (patients)	10	4	0.01‡

*Paired t test.
†Unpaired t test.
‡χ^2.

cases, which seldom exceed 10% of NICU admissions, the most commonly found pathogen is *Streptococcus agalactiae* (Group B).[1,4-6] During the first week of life the percentage of infants whose tracheas were colonized ranged from 10% to the 23% reported here. Colonization of the proximal airways is delayed by the administration of antibiotics and increases in direct relation to the duration of the intubation. Our data indicate that in about 3 weeks the majority of intubated newborns have acquired bacterial flora in their trachea. Several years ago, it was feared that this colonization would result in an increased risk for infection.[19,20] Recent investigations,[4-6] including the present study, have shown that not to be the case.

In spite of the vast number of mechanically ventilated infants, the pattern of tracheal colonization relative to the various environments and treatments has not been extensively studied. The presence of yeast in TA taken during the first week is not unexpected, and its observed disappearance over time is consistent with earlier reports.[21] The ratio of Gram-positive cocci to Gram-negative bacilli from TAs remained essentially unchanged throughout our study period—2:1. This is in contrast to the experience of Slagle et al[4] who observed a significant rise in the number of cultures of Gram-negative bacilli after four weeks of ventilation.

In the past, there has been some concern about the possible effect of exogenous surfactant on the pulmonary host defenses.[2] In a rabbit model of pneumonia, it was shown that surfactant was not detrimental to lung defenses and one specific preparation (Exosurf) significantly reduced the growth of *S agalactiae*.[22] The incidence of sepsis and pneumonia has not been noted to increase following the administration of natural or synthetic surfactant.[10-13,15] Our results also indicate that the administration of Exosurf did not alter the pattern of tracheal colonization in intubated newborns, nor did it increase the incidence of neonatal infections. However, the consequences of giving surfactant to neonates with congenital pneumonia are still unclear.

It is generally accepted that long-term corticosteroid treatment is associated with an increased susceptibility to infections in adults and children.[23] Thus, it is not surprising that the practice of treating infants with BPD with dexamethasone has been regarded with some apprehension. Early investigators reported several cases of neonatal sepsis; whereas, more recently, others[9,15,23] concluded that corticosteroid treatment did not modify the incidence of infections. Our data support the latter conclusion.

Intravascular catheter placement has been associated with an increased risk of infections, especially in the small premature infant.[24-27] The 34% incidence of culture-proven sepsis among patients in whom CVCs were placed, the predominance of Gram-positive cocci among the isolates, and the absence of sepsis-related mortality is comparable to that reported by others.[24,26] Tracheal colonization patterns were similar in patients who had CVCs and those who did not, regardless of whether those patients later became septic. This observation seems to exonerate the tracheobronchial mucosa as a portal of entry for CVC-associated septicemia and reaffirms the commonly accepted notion of peripheral bacterial contamination.

Even when performed daily, TA surveillance has shown to be of limited value in the prediction and/or management of late-onset sepsis.[3-6] Like others, we have observed that patterns of tracheal bacterial colonization are almost identical between infants who did and those who did not develop late-onset septicemia. It can be argued that weekly TA cultures can detect the introduction and spread of pathogens. Furthermore, detection of background flora changes and antibiotic sensitivity of potential pathogens could be helpful in formulating NICU antibiotic coverage policies.[2]

Conclusions

Tracheal colonization of the mechanically ventilated neonate in the NICU setting appears to be related to environmental exposures and is not influenced by treatment modalities or manipulations such as exogenous pulmonary surfactant and systemic dexamethasone therapy and central venous catheterization. TA cultures are of limited value in predicting the likely occurrence or the etiology of late-onset infections such as pneumonia or septicemia. TA cultures performed at weekly intervals can assist in monitoring the impact of NICU exposures on the outcome in a specific infant population. The recognition of the introduction or spread of bacterial pathogens allows for timely infection control interventions such as infant isolation, staff edu-

cation, or review of antibiotic programs. Based on data from this study, septicemia of the newborn is significantly associated with birthweight, gestational age, and central venous catheterization.

PRODUCT SOURCES

Conventional Mechanical Ventilator:
Sechrist IV 100 B, Sechrist Industries Inc, Anaheim CA

High Frequency Flow Interrupter:
Infant Star Neonatal High Frequency Ventilator, Infrasonics Inc, San Diego CA

Pulmonary Surfactant:
Exosurf, Burroughs Wellcome Co, Research Triangle Park NC

Central Venous Catheter:
Broviac Single-Lumen Vascular Access Catheter, Bard Access Systems, Salt Lake City UT

Statistical Software:
BMDP Statistical Software Inc, Los Angeles CA

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CORRECTION

In the October issue of the Journal [Respir Care 1993;38(10):1110], we published a review of the book "Respiratory Care: A Guide to Clinical Practice," 3rd edition, by George E Burton, John E Hodgkin, and Jeffrey J Ward. We incorrectly gave the price of this volume at $150.00; according to the publisher, the correct price is $67.50. We regret the error.

Antimuscarinic and β_2-Adrenoceptor Bronchodilators in Obstructive Airways Disease

Cynthia L Howder BS RRT CPFT

I. INTRODUCTION
II. REGULATION OF AIRWAY CALIBER AND BRONCHOMOTOR TONE
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  B. Parasympathetic (Cholinergic) Nervous System
    1. Structure and Function in the Airways
    2. Antimuscarinic Agents (Anticholinergics, or Parasympatholytics)
  C. Sympathetic Nervous System
    1. Structure and Function in the Airways
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INTRODUCTION

The therapeutic efficacy of inhaled bronchodilators in the management of patients with airflow obstruction (chronic bronchitis, emphysema, and asthma) is a subject of continuing academic and clinical interest. Two primary types of inhaled bronchodilators are administered to patients with airflow obstruction: the β_2-adrenoceptor agonists and the antimuscarinic (anticholinergic) agents. When one is presented with bronchodilators that exert pharmacologic influences by different mechanisms, several questions arise: Is one more effective than the other? Will beneficial effects be additive if the two types are administered together? Does a patient's particular disease condition dictate the choice of one over the other?

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To help answer these questions, in this review I (1) examine the autonomic regulation of airway function and the pharmacology of the inhaled bronchodilators, (2) review relevant clinical literature concerning the use of these agents in patients with airflow obstruction, and (3) review the factors that precipitate airway obstruction and the type of bronchodilator more effective to reverse the obstruction. A better understanding of these three vital aspects can guide the clinician to choose a drug regimen that is appropriate and effective for a specific patient.

REGULATION OF AIRWAY CALIBER AND BRONCHOMOTOR TONE

Airway smooth muscle tone is regulated by the three components of the autonomic nervous system—the sympathetic (adrenergic), the parasympathetic (cholinergic), and the nonadrenergic non-

cholinergic (NANC) systems.[1,2] In addition to regulating airway smooth muscle tone, the autonomic nerves influence secretion of mucus from submucosal glands, vascular permeability and blood flow, fluid transport across airway epithelium, and release of mediators from mast cells and other cells that participate in the inflammatory response.

Nonadrenergic Noncholinergic Nervous System

Although comparatively little is known or written about the third neural pathway, the NANC nervous system, results of various studies establish its presence in the airways of the lungs from the trachea to the smallest bronchi.[3-5] The NANC system, also known as the nonadrenergic inhibitory nervous system, is believed to be the primary inhibitory system in the airways[3,4]—inhibitory in that it prevents bronchial smooth muscle contraction. (There is minimal innervation of the airways by the sympathetic nervous system; therefore, the sympathetic nerves do not have a direct role in inhibition of airway smooth muscle contraction.[3]) The neurotransmitters of this third nervous system remain to be clearly defined; however, increasing evidence exists that vasoactive intestinal peptide (VIP) and peptide histidine methanol are the primary mediators of the NANC system.[4,6] Functional VIP receptors have been localized to airway smooth muscle, epithelial cells, and submucosal glands.[7,8] Stimulation of VIP receptors initiates a mechanism in which adenyl cyclase catalyzes the conversion of adenosine triphosphate (ATP) to cyclic 3′,5′-adenosine monophosphate (cAMP); cAMP then triggers a sequence of intracellular events that ultimately produces relaxation of airway smooth muscle (Fig. 1).[7,9]

Endogenous VIP is a highly potent airway smooth muscle relaxant; however, inhaled VIP has little efficacy as a bronchodilator and exhibits minimal protective effects against histamine-induced bronchoconstriction when compared to β_2-adrenoceptor agonists.[10] The absence of a bronchodilating effect from inhaled VIP may be due either to enzymatic breakdown of the peptide or to its inability (because of its relatively large size) to gain access to its receptors in airway smooth muscle. Some investigators have suggested that a defect or disturbance in the NANC system might provide an explanation for the hyperreactive airways of asthma and chronic bronchitis due to the loss of control of normal smooth muscle tone.[3,5]

Parasympathetic (Cholinergic) Nervous System

Structure & Function in the Airways

The predominant neural control of bronchomotor tone and submucosal gland secretion is through the vagally mediated pathways of the parasympathetic

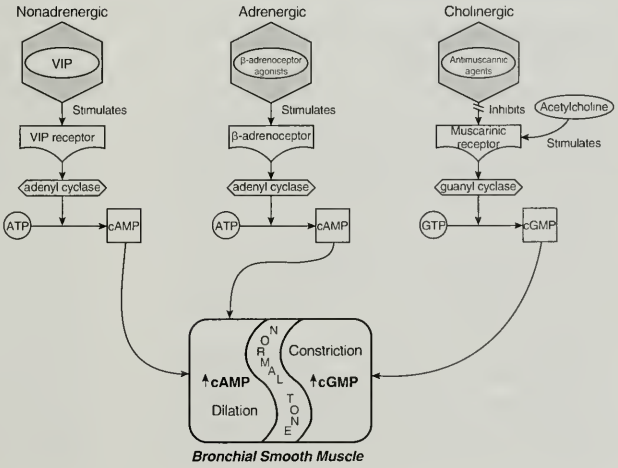


Fig. 1. Physiologic and pharmacologic control of bronchomotor tone.

nervous system.[1,2,11] When stimulated, the vagal efferent nerves release the neurotransmitter acetylcholine from the presynaptic nerve terminals. Acetylcholine diffuses across the synaptic cleft and binds to the muscarinic (cholinergic) receptors located in or adjacent to the respiratory epithelium, submucosal glands, mast cells, and airway smooth muscle.[12-14] Autoradiographic mapping of muscarinic receptors has demonstrated a high density of these receptors in the smooth muscle of large central airways.[14,15] The density of these receptors decreases as the airways become smaller; thus, both proximal and distal bronchioles are nearly devoid of receptors. After attachment of acetylcholine to the muscarinic receptor, a series of enzymatic reactions is initiated in which guanyl cyclase catalyzes the conversion of guanosine triphosphate (GTP) to cyclic 3′,5′-guanosine monophosphate (cGMP). An increase in the level of intracellular cGMP elicits an excitatory reaction in the lung, producing bronchial smooth muscle contraction and increased bronchial gland secretion (Fig. 1).[16,17] In response to acetylcholine, various chemical mediators that abide within mast and various inflammatory cells are also released (eg, histamine, chemotactic factors, and the arachidonic acid metabolites: the leukotrienes, prostaglandins D_2 and $F_{2\alpha}$, and platelet activating factor).[13] These mediators initiate the inflammatory response in the lung—smooth muscle spasm, mucus secretion, and mucosal edema.

Antimuscarinic Agents (Anticholinergics, or Parasympatholytics)

Antimuscarinic agents competitively inhibit acetylcholine from binding to the muscarinic receptor (Fig. 2),[18] which, in turn, produces a parasympathetic (vagal) blockade.[1-3] This action results in bronchodilation and a decrease in the production of tracheobronchial secretions. Results of several clinical trials indicate that the major site of bronchodilator action for inhaled antimuscarinic agents is in the large central airways.[19-27]

The rationale for administering antimuscarinic agents to patients with airflow obstruction is based on two primary postulates:[28] (1) cholinergic mediation of bronchospasm is considered a primary mechanism of airflow obstruction in some patients

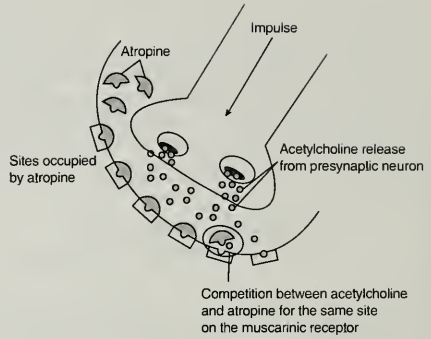

Impulse
Atropine
Sites occupied by atropine
Acetylcholine release from presynaptic neuron
Competition between acetylcholine and atropine for the same site on the muscarinic receptor

Fig. 2. Graphic presentation of competitive inhibition by atropine. (From Reference 18, with permission.)

and (2) airflow obstruction can be inhibited and/or reversed pharmacologically with antimuscarinic agents.

Atropine, the prototypic antimuscarinic agent, is a tertiary ammonium alkaloid commonly used as the sulfate salt. The plasma half-life is 2-3 hours and the drug is eliminated by hepatic metabolism. Following an aerosol dose, onset of action usually occurs within 15 minutes and peak effects in 60-120 minutes. The duration of action of atropine sulfate is 3-5 hours depending on the dose administered.[29,30] Following administration, atropine is widely distributed in the body and may elicit systemic side effects.[31] As the dosage of atropine is increased, important adverse effects may result, including tachycardia, urinary retention, transient headache, visual blurring, mental confusion, depressed ciliary transport, and depressed mucociliary clearance.[23,29,31-34] The optimal effective aerosol dose of atropine sulfate with the least side effects has been reported to be 0.025 mg/kg in adults[29] and 0.05 mg/kg in children with airways obstruction.[30] At these therapeutic doses, dryness of the mouth is the most common side effect.

Atropine methonitrate (methylnitrate quaternary salt of atropine) has properties similar to those of atropine sulfate with two notable exceptions: It is twice as potent as atropine and has a longer duration of activity.[35] A 2-mg dose of atropine methonitrate in combination with fenoterol (0.4 mg) produces an increase in FEV_1 in asthmatic patients similar to that produced by 4 mg of atropine sulfate in combi-

nation with 0.4-mg fenoterol. In the study by Allen and Campbell,[35] the response to the atropine methonitrate combination also produced a significant increase in the FEV_1 for 6 hours, whereas the increase in the FEV_1 with the atropine sulfate combination was 4 hours. The recommended therapeutic dose of atropine methonitrate is 1.5 mg.[36,37] At this dose, onset of action occurs between 15 and 30 minutes and peak effects between 1 and 2 hours, with a duration of activity of 4-6 hours.[35-37] Atropine methonitrate does not cross the blood-brain barrier; therefore, systemic side effects are minimal, even with an inadvertent overdose.[38] Atropine methonitrate is popular in Europe where it is also known as methylatropine nitrate.

Glycopyrrolate is a semisynthetic quaternary ammonium compound that has an onset of action of 15-30 minutes. A therapeutic dose of 1.0 mg produces a peak response within 30-60 minutes. Glycopyrrolate has a relatively long duration of activity of 6-8 hours.[39,40] Like all quaternary ammonium salts, glycopyrrolate does not cross the blood-brain barrier and, therefore, has minimal cardiovascular and central nervous system side effects when compared to atropine.[39-41] Glycopyrrolate methylbromide (Robinul) is currently (1993) under study as an aerosolized antimuscarinic bronchodilator; the injectable solution (0.2 mg/mL) is used for aerosol administration.[39-41]

Ipratropium is a quaternary isopropyl derivative of atropine. When administered by inhalation, significant bronchodilation usually occurs within minutes.[27,42-45] Ipratropium usually produces 50% of the maximal bronchodilator response within 3 minutes, 80% within 30 minutes, and 100% at 1-2 hours.[44,45] Ipratropium does not cross the blood-brain barrier as atropine does; therefore, it is a relatively safe bronchodilator when used in prescribed therapeutic doses.[46,47] Optimal bronchodilation is achieved by doses of 0.04-0.08 mg with a resultant duration of activity of 4-6 hours.[27,42,45,48] Side effects of ipratropium are minimal owing to poor systemic absorption from the respiratory tract;[46] dryness of the mouth is the most commonly reported side effect, and disturbed vision (after spraying a part of the dose into the eyes) has also been reported.[49] Ipratropium does not depress ciliary activity, change sputum viscosity, or retard mucociliary clearance as does atropine.[45,46,50] By inhalation, ipratropium (0.04 or 0.08 mg) is as effective a bronchodilator as atropine (2 mg)[51] with a 30-50% longer duration of effectiveness.[46] Ipratropium bromide (Atrovent) is available for inhalation administration in metered-dose inhaler (MDI) form. Ipratropium in combination with fenoterol (Duovent, Berodual) is available abroad. This combination provides for simultaneous administration of an antimuscarinic and a β_2 agonist.

Oxitropium bromide, a quaternary ammonium derivative of scopolamine (hyoscine), is a relatively new antimuscarinic agent marketed abroad under the trade names of Oxivent, Tersigat, Ventilat, and Ventox. Oxitropium is less potent than ipratropium (0.2 mg of oxitropium is equivalent in effectiveness to 0.08 mg of ipratropium).[52] However, oxitropium has a longer duration of activity than ipratropium, producing bronchodilation for as long as 8-10 hours.[52-54] In patients with chronic bronchitis, Peel and Anderson[53] found 0.4-0.6 mg of oxitropium to be the optimal dose range, whereas Skorodin and colleagues[54] documented an optimal dose range of 0.1-0.4 mg. Side effects reported in Peel and Anderson's[53] clinical trial with 12 patients were dryness of mouth (3 patients, 0.6-mg dose), unpleasant taste (4 patients, at the higher doses), and headache (2 patients, 1 at the 0.2-mg dose and 1 at the 0.4-mg dose). No side effects were reported in Skorodin and colleagues' study of 14 bronchitic patients.[54] Other clinical trials have shown that a dose of 0.2 mg is optimal for eliciting a maximal response and prolonged duration of activity (up to 10 hours).[52,55,56] Onset of action of oxitropium varies from 5-15 minutes with peak effects occurring at 1-2 hours. Oxitropium does not adversely affect mucociliary clearance, sputum production, or sputum viscosity.[57] Table 1 summarizes the characteristics of the antimuscarinic agents discussed in this section.

Sympathetic Nervous System

Structure and Function in the Airways

The principal nervous pathways in the airways are excitatory (the cholinergic system) and inhibitory (the NANC system).[1,3,4] The physiologic significance of the sympathetic nerves in regulating bronchomotor tone has not been clearly defined.

Table 1. Aerosol Antimuscarinic Agents

Drug	Preparations	Dosages	Onset (min)	Peak (min)	Duration (h)
Atropine sulfate	Solution: 0.5% (5 mg/mL) Solution: 0.2% (2 mg/mL)	0.025 mg/kg tid, qid (adult); 0.05 mg/kg tid, qid (child)	15	60-120	3-5
Atropine methonitrate	Solution: 0.5% (5 mg/mL)	1.5 mg tid, qid	15-30	60-120	4-6
Glycopyrrolate (Robinul)	Solution: 0.02% (0.2 mg/mL) (injectable solution)	1 mg tid, qid	15-30	30-60	6-8
Ipratropium bromide (Atrovent)	MDI: 0.018 mg/spray MDI: 0.02 mg/spray Solution: 0.025% (0.25 mg/mL)	2 puffs tid, qid; up to 4 puffs tid, qid 0.25-0.5 mg q 4-6 h	3-15	60-120	4-6
Oxitropium bromide (Oxivent, Tersigat, Ventilat, Ventox)	MDI: 0.1 mg/spray	2 puffs bid, tid	5-15	60-120	8-10

Sympathetic innervation is essentially nonexistent in airway smooth muscle,[3,58] yet the sympathetic system innervates the ganglia of both sympathetic and parasympathetic systems, submucosal glands, and vascular smooth muscle.[58,59] Some investigators suggest that the sympathetic neural system indirectly influences bronchomotor tone through interaction with parasympathetic pathways at the ganglionic level and/or by causing the release of norepinephrine.[1,4]

Autoradiographic studies have shown that the airways are well populated with β_2 adrenoceptors, with a high density of these receptors in the smaller, peripheral airways.[15,60] β_2 adrenoceptors have also been found in airway epithelium, alveolar walls, vascular smooth muscle, and submucosal glands.[60] Endogenous catecholamines (the presynaptic neurotransmitter norepinephrine or epinephrine secreted by the adrenal medulla) or exogenous β_2 agonists (drugs) have the ability to stimulate and activate the β_2 adrenoceptors.[16,17] The sequence of events that occurs when β_2 adrenoceptors are stimulated is similar to that occurring with VIP receptor stimulation: Adenyl cyclase is activated and then catalyzes the conversion of adenosine triphosphate (ATP) to cyclic 3′,5′-adenosine monophosphate (cAMP). As mentioned previously, it is the level of intracellular cAMP that is responsible for the relaxation of airway smooth muscle (Fig. 1).

Autoradiographic studies have also determined the presence of β_1 and α adrenoceptors in the lung.[15,60] β_2 and β_1 adrenoceptors coexist in an approximate ratio of 3:1 in bronchial submucosal glands and alveolar walls, whereas only β_2 adrenoceptors are found in large and small airways, airway epithelium, and vascular smooth muscle.[60] The importance of the presence of β_1 adrenoceptors in the lung remains to be determined. Numerous α adrenoceptors are found in small bronchioles but are relatively sparse in large airways.[15] α adrenoceptor stimulation produces vasoconstriction, bronchoconstriction, and increases in glandular secretions.[13,61] Treatment of asthmatic patients with α adrenoceptor blocking agents to counteract the bronchoconstrictive effects of the α adrenoceptor is not usually therapeutically effective.[62]

β_2-Adrenoceptor Agonists (Sympathomimetics)

Knowledge of the value of adrenergic or sympathomimetic therapy for the treatment of reversible bronchospasm dates back to the turn of the century when Solis-Cohen[63] used desiccated adrenal glands to treat asthma. β_2 agonists are potent bronchodilators, and this bronchodilation represents the main therapeutic effect of β_2 drugs.[64,65] Secondary beneficial actions are also noted with these agents: They

inhibit antigen-induced release of mast cell mediators,[66,67] reduce vascular permeability,[68] and enhance the mucociliary transport of respiratory secretions.[69] Increasing evidence exists that β_2-adrenoceptor-mediated bronchodilation requires penetration of the aerosol into the smaller, peripheral airways.[19,20,22,70,71]

Epinephrine, the forerunner of all the sympathomimetic bronchodilators, has been utilized in aerosol form since the early 1900s. β_2-agonist administration by inhalation is commonly preferred because onset of action is very rapid (generally noted within 5-15 minutes); inhalation delivers the drug directly to the desired site of action, the airways; systemic side effects are minimal when these agents are administered in prescribed therapeutic doses; and administration by inhalation requires much smaller doses to achieve a desired therapeutic response.[72] The primary disadvantage of the inhaled route is that in patients who are not mechanically ventilated a great deal of cooperation is required to deliver the drug adequately to the smaller, peripheral airways where the largest numbers of β_2 adrenoceptors are located.[15,60,73] In patients with severe bronchospasm, mucus plugging, or lobar consolidation, the drug may not be deposited distal to the obstruction. In some cases, such as patients with severe bronchospasm, much larger doses may be required to achieve satisfactory results.[74] Another consideration is that a high percentage of each drug dose commonly gets trapped in the upper airways or is swallowed. Approximately 9-11% of a dose from an MDI and a mean of 12% (range 3.9-18.3%) of a dose administered by nebulization is retained within the lungs.[75,76]

Three classes of sympathomimetic bronchodilators are available for aerosol administration in the United States: catecholamines, resorcinols, and saligenins.[64,65]

The catecholamine class of aerosol bronchodilators includes epinephrine and the synthetic derivatives: isoproterenol, isoetharine, rimiterol, and hexoprenaline. Rimiterol (Pulmadil) and hexoprenaline (Ipradol) are available abroad. Epinephrine, isoproterenol, and isoetharine were the only approved β-adrenergic aerosol bronchodilators for many years until several analogues (catecholamine derivatives) became available and were approved for use in the United States.[64] Epinephrine is a highly potent stimulator of α and β adrenoceptors. Isoproterenol has equal affinity for both β subtypes, whereas isoetharine preferentially stimulates β_2 adrenoceptors with little or no action on α adrenoceptors.[64]

Although effective and potent (isoproterenol is ranked highest in potency as a β stimulant), the catecholamine class of bronchodilators has two primary disadvantages for use in patients with airflow obstruction. First, the catecholamines are severely limited in their duration of effectiveness (1-3 hours at most), being rapidly metabolized by the cytoplasmic enzyme catechol-O-methyltransferase (COMT).[64,65] Second, the catecholamines elicit undesirable dose-dependent side effects because of their ability to also stimulate the α and/or β_1 adrenoceptors.[72,77-79] Adverse reactions noted with these drugs include palpitations, tachycardia, increased blood pressure, skeletal muscle tremor, headache, dizziness, irritability, anxiety, insomnia, nausea, and worsening of the match of ventilation and perfusion within the lung ($\dot{V}/\dot{Q}$ mismatch) with consequent decrease in P_{aO_2} (noted with isoproterenol administration[80,81]). Metabolic derangements such as hypokalemia have also been noted with these agents, as well as with the newer β_2-selective agonists. A primary concern in this reaction is hypokalemia-induced dysrhythmias.[82-84]

Bitolterol, a sympathomimetic bronchodilator approved for clinical application in the United States, differs from the previous agents mentioned in that it is converted to its active catecholamine compound, colterol, in the body.[85,86] The process of hydrolysis is slow, gradually releasing the active catecholamine. By this mechanism, a sustained duration (up to 8 hours) results. Once fully activated, colterol may be metabolized by COMT. Bitolterol is noted to have fewer cardiovascular side effects compared to the other sympathomimetics of the catecholamine class.[85,86]

The recommended doses, onset of action, peak effects, and duration of activity of the catecholamines are summarized in Table 2.

Since the mid-1960s the direction of development of sympathomimetic bronchodilators has been toward safe, β_2-specific, longer-acting agents. Distinctions between the various β_2 agonists are based on differences in chemistry and on selectivity for the β_2 adrenoceptor over the β_1 adrenoceptor. Modification of the primary catechol nucleus has result-

Table 2. Aerosol Beta$_2$-Adrenoceptor Agonists*

Drug	Preparations	Dosages	Onset (min)	Peak (min)	Duration (h)
Catecholamines:					
Epinephrine (Asthmahaler, Bronitin Mist, Bronkaid Mist, Primatene Mist, Medihaler-Epi, Adrenalin)	MDI: 0.16, 0.2, 0.27 mg/spray Solution: 1% (10 mg/mL)	1-2 puffs qid 2.5-5.0 mg qid	3-5	5-20	1-3
Isoproterenol (Isuprel, Vapo-Iso, Medihaler-Iso)	MDI: 0.08, 0.11, 0.12, 0.13 mg/spray Solution: 1% (10 mg/mL) 0.5% (5 mg/mL 0.25% (2.5 mg/mL)	1-2 puffs qid 1.25-2.5 mg qid	2-5	5-30	0.5-2
Isoetharine (Bronkometer, Bronkosol)	MDI: 0.34 mg/spray Solution: 1% (10 mg/mL) 0.5% (5 mg/mL)	1-2 puffs qid 2.5-5.0 mg qid	1-6	15-60	1-3
Bitolterol (Tornalate)	MDI: 0.37 mg/spray	2-3 puffs q 4-6 h; or 2 puffs q 8 h	3-4	30-60	5-8
Resorcinols:					
Metaproterenol (Alupent, Metaprel)	MDI: 0.65 mg/spray Solution: 5% (50 mg/mL) 0.6% (6 mg/mL)†	2-3 puffs q 4 h 0.3 mL (15 mg) q 3-4 h	1-5	30-60	3-4
Terbutaline (Brethaire, Brethine, Bricanyl)	MDI: 0.2, 0.25 mg/spray Solution: 1% (10 mg/mL)	2 puffs q 4-6 h 5-10 mg q 4-6 h	5-30	30-60	3-6
Fenoterol (Berotec)	MDI: 0.1, 0.2 mg/spray Solution: 0.5% (5 mg/mL)	1-2 puffs bid, tid 0.5-1.25 mg qid	5	30-60	3-6
Saligenins:					
Albuterol, Salbutamol (Proventil, Ventolin)	MDI: 0.09, 0.1 mg/spray Solution: 0.5% (5 mg/mL) 0.1% (1 mg/mL) 0.083% (0.83 mg/mL)†	2 puffs q 4-6 h 2.5 mg q 4-6 h	< 15	30-60	3-6
Pirbuterol (Maxair)	MDI: 0.2 mg/spray	1-2 puffs q 4-6 h	5	30-60	3-5
Carbuterol (Bronsecur)	MDI: 0.1 mg/spray	1-2 puffs q 3 h	5-10	60	3-4
Newer Agents:					
Procaterol (Pro-Air)	MDI: 0.01 mg/spray	2 puffs tid	2-5	30-60	6-8
Salmeterol (Serevent)	MDI: 0.025 mg/spray	2 puffs bid, up to 4 puffs bid	13-18	180-240	12-18
Formoterol	MDI: 0.006 mg/spray	2 puffs bid	1-5	60-180	> 12

*Solutions for nebulization are concentrated and must be diluted with sterile sodium chloride 0.9% solution prior to administration.
†Packaged as a unit dose—requires no dilution prior to administration.

ed in the β_2-specific resorcinol and saligenin groups of sympathomimetic bronchodilators. An added benefit with these bronchodilators is their longer duration of activity. Because they lack a catechol nucleus they are not vulnerable to COMT.

The resorcinol class of sympathomimetic bronchodilators includes metaproterenol, terbutaline, and fenoterol. Metaproterenol, reported for the treatment of asthma in the early 1960s, was the first resorcinol derivative marketed. Terbutaline and fenoterol then followed. Fenoterol is not commercially available in the United States, whereas metaproterenol and terbutaline are. Terbutaline and fenoterol are about equally potent.[87-89] As mentioned, resorcinols are resistant to metabolism by COMT and thus have a relatively longer duration of action (3-6 hours) compared to the catecholamines. Fenoterol and terbutaline are more highly β_2 selective, with a longer duration of activity than metaproterenol.[90-92] Although fenoterol is a highly effective β_2 agonist, concerns regarding fenoterol's margin of safety have been raised. Recent studies have linked the regular and long-term use of fenoterol with an increased risk of death or near-death in asthmatic patients.[93,94] In addition, fenoterol has been shown to cause more adverse cardiac effects and a greater reduction in plasma potassium concentration than albuterol, terbutaline, or isoproterenol.[82,95] The recommended dose of fenoterol has been revised in the current issue of the *British National Formulary*.[96] Patients are strongly cautioned not to exceed their prescribed dose. The pharmacologic aspects of the resorcinol class of sympathomimetics are summarized in Table 2.

Albuterol (salbutamol in Europe), pirbuterol, and carbuterol are sympathomimetic bronchodilators of the saligenin class. β_2 specificity, minimal cardiac effects, and a long duration of activity are noted features of this class of drugs. Onset of action of albuterol is noted to occur within 15 minutes and peak effect in 30-60 minutes; the duration of effectiveness is up to 6 hours.[77-79,97,98] Inhaled pirbuterol has an onset of activity within 5 minutes and peak effect in 30-60 minutes; the duration of effectiveness is up to 5 hours.[99,100] Pirbuterol is currently available for inhalation only in MDI form, whereas albuterol is available both in MDI form and as a solution for nebulization (Table 2). Carbuterol, marketed abroad, has pharmacologic effects similar to albuterol but is less potent and has a shorter duration of effectiveness (approximately 4 hours).[91,101] For these selective β_2 agonists, the most common side effects are skeletal muscle tremor and palpitations.

Procaterol is a recent addition to the β_2-specific agents. Currently available in Canada, procaterol exhibits a higher potency and longer duration of activity (up to 8 hours) than albuterol. Onset of action is within 5 minutes, and peak effects occur 30-60 minutes after administration. Procaterol is marketed under the trade name of Pro-Air.[102,103]

Two highly potent sympathomimetic bronchodilators that seem to have a promising future for β_2-adrenoceptor therapy are salmeterol and formoterol. Numerous clinical trials have compared the pharmacologic properties of salmeterol with those of albuterol.[104-110] The consensus of those investigators is that salmeterol is a superior β_2 agonist in both efficacy and duration of activity. Salmeterol produces a greater and more sustained increase in respiratory function with a duration of activity 2 to 3 times that of albuterol (12 or more hours in most cases). At least one group of investigators[105] has come to refer to albuterol as the "short-acting" β_2 agonist, a term that had never been associated with albuterol until the advent of salmeterol. The salmeterol-treated group of asthmatic patients experienced fewer symptoms of asthma and related events than did the albuterol-treated group. The optimal therapeutic dose of salmeterol is 0.05 mg twice daily (up to 0.1 mg twice daily for severe airway obstruction).[104,107-111] Smyth and colleagues[109] indicate that salmeterol may be up to 10 times more potent than albuterol; 0.05 mg of salmeterol administered twice daily may be as effective as albuterol 0.5 mg administered every 4-6 hours. The one drawback to salmeterol is that it has a slower onset of action than albuterol. In Simons and associates' study,[108] the increase in FEV_1 was significantly lower for salmeterol than for albuterol for the first one-half hour after administration. However, from 3-12 hours after administration, salmeterol's response greatly exceeded that of albuterol. Due to salmeterol's slower onset of action, an unusual characteristic for a β_2 agonist, salmeterol is not indicated for the rapid relief of acute bronchospasm.[111] Regardless of the slower onset of action, a significantly lower incidence in nocturnal and daytime symptoms in salmeterol-treated asthmatics has been noted;[104] therefore,

salmeterol is suitable for stable asthmatics or for those who experience nocturnal asthma. Adverse reactions to salmeterol are infrequent and mild; tremor and palpitations were reported in some of the patients who were administered higher doses.[106] Like other β_2 agonists, salmeterol reduces vascular permeability, inhibits the release of mediators, and enhances mucociliary function.[112] Yet, unlike the other β_2 agonists, salmeterol exhibits this stimulatory effect with a higher efficacy for up to 12 hours.

Formoterol has pharmacologic properties similar to salmeterol. Formoterol also exhibits a high affinity and selectivity for the β_2 adrenoceptor with a duration of activity in excess of 12 hours.[113-122] Twelve μg of formoterol is equipotent with 50 μg of salmeterol.[113] However, unlike salmeterol, formoterol has the clinical advantage of a rapid onset of action. Within 1 minute after inhalation, formoterol produces a significant improvement in respiratory function.[116,118,119] The most commonly reported side effect is tremor, especially noted in doses higher than 12 μg.[118] Studies comparing the pharmacologic effects of formoterol with those of albuterol produced results similar to results of studies comparing salmeterol with albuterol.[120-122] These studies reported that the formoterol-treated patients not only had a sustained improvement in respiratory function, but also had less daytime and nocturnal asthma symptoms than the albuterol-treated patients.

The recent development of these new β_2 agonists with a duration of action in excess of 12 hours may well change the strategies for the treatment of bronchial asthma. These bronchodilating agents have not only brought a new concept to bronchodilator pharmacology but also have given clinicians viable alternatives for safe, effective, and long-lasting pharmacologic manipulation of airway caliber.

Some investigators have found that repeated and frequent dosing with a β_2 agonist leads to a decreased responsiveness or duration of effectiveness to subsequent doses; the end-result may be that the drug must be discontinued or the patient may need a higher dose of the drug in order to elicit the same effect noted with the initial dose.[93,94,123-136] The decreased responsiveness or duration of effectiveness is known as developing a tolerance (subsensitivity) to the drug. Rapidly developing tolerance is called tachyphylaxis. Tolerance and tachyphylaxis are key issues of concern for many clinicians worldwide who prescribe β_2 agonists for their patients with acute or chronic airflow obstruction. Subsensitivity resulting from continuous and prolonged administration of β_2-adrenoceptor stimulants is a hotly debated issue. Subsensitivity and other adverse effects noted with β_2-adrenergic therapy (such as rebound bronchoconstriction, cardiotoxicity, and hypokalemia-induced dysrhythmias have been linked to the rise in asthma deaths.[93-95,123] Several clinical trials have documented that drug tolerance or rebound bronchoconstriction does exist, not only with the catecholamine class of bronchodilators[123-127] but also with the more β_2-selective agonists: terbutaline,[128,129] albuterol,[130-132] fenoterol,[93,94,133,134] and salmeterol.[135,136] A recent clinical trial conducted by van Schayck and colleagues[131] compared the long-term effects of inhaled bronchodilator use in two groups of patients: One group consisted of those patients who used albuterol or ipratropium on a regular basis for 2 years, whereas the other group consisted of those patients who for 2 years used the bronchodilators only when symptomatic. The annual decline in pulmonary function was greater in the group who used the bronchodilators on a regular basis than in the group who used the bronchodilators only as needed.

On the other end of the spectrum are those clinical trials that have failed to find that tolerance or tachyphylaxis develops in response to long-term, continuous β_2-adrenoceptor therapy, especially with the newer and improved β_2 agonists.[104,105,110,114,117,120,137-144] The conclusions stated from some investigators are (1) that the loss of an effective response is not due to tolerance to the β_2 agonist but may be due to obstruction from airway inflammation as the disease becomes more severe, and (2) that effective β_2-agonist therapy may mask increased severity of the disease.[65,107,120] Some maintain that should tolerance develop, it is mild, of minimal clinical relevance, and transitory in that the response to the β_2 agonist reverts back to its usual level after treatment with corticosteroids or after discontinuance of the adrenergic drug for a few days to a few weeks.[111,130] Within 1 hour after intravenous administration of corticosteroids, β_2-adrenoceptor responsiveness can be re-established, and concurrent corticosteroid therapy (oral or inhaled) with β_2-adrenoceptor therapy may reduce the risk for the development of tolerance.[111,120,128,144,145] Although a

change in β_2 agonist has also been suggested should tolerance occur, if tolerance has developed in the administration of one β_2 agonist, it may well occur with all β_2 drugs—in general or of that particular class with which the patient has been treated ("cross-tolerance").[126,129,146] A rare effect of inhaled catecholamines (specifically isoproterenol) is the paradoxic bronchoconstrictor response[147,148] observed in some patients with status asthmaticus.[149] Tolerance should not be mistakenly blamed for this occurrence.

Because of the controversy surrounding the long-term, continuous use of β_2-agonist therapy, some clinicians advise that β_2-agonist therapy be used only on an as-needed basis for symptom relief.[93,94,131] The reader is encouraged to read the debate between Ziment[150] and Skorodin[151] concerning β_2-agonist tolerance, rebound bronchoconstriction, and tachyphylaxis.

COMPARATIVE BRONCHODILATOR STUDIES

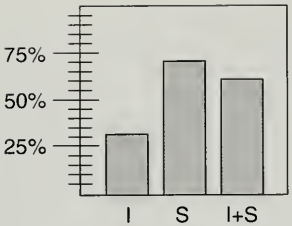
Many clinical trials have compared the efficacy of various antimuscarinic agents to various β_2 agonists. The studies summarized in Figures 3[134,155-162] and 4[155,157,161,163-167] and discussed further in this paper meet several specific criteria: They compared the effects of inhaling the antimuscarinic agent ipratropium bromide alone with the effects of inhaling a newer second- or third-generation β_2 agonist alone, and compared those effects with the effects of inhaling the two agents in combination. In the studies selected, the type of airflow obstruction was clearly documented as a clinical diagnosis (many diagnoses were based on the criteria set by the American Thoracic Society [1987],[152] the Medical Research Council criteria for chronic obstructive bronchitis [1965],[153] and/or the criteria set by the Ciba Guest Symposium [1959][154]).

Analysis of Comparative Trials of Patients with Asthma

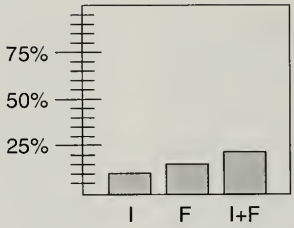
The results of the 9 studies shown in Figure 3 demonstrate that the β_2 agonist is a superior bronchodilator with mean improvement of 33% (15-71% range) above pretreatment baseline FEV_1 or PEFR when compared with the antimuscarinic agent with mean improvement of 21% (10-36% range) above baseline, in the asthmatic patient. An exception is noted in the study of Storms and colleagues,[168] a multicenter 90-day trial of 144 stable asthmatics. The results of this study suggest that both aerosols are equally effective bronchodilators. Throughout the entire 90-day study, metaproterenol maintained a faster onset of action than ipratropium, but ipratropium produced a longer duration of effectiveness. This study was not included in Figure 3 because the investigators did not administer combination therapy, yet it is important because it was a long-term trial of a large patient population.

An overview of this group of studies suggests that when ipratropium and a β_2 agonist are given together by inhalation, the bronchodilator effect is additive in the asthmatic patient. Some investigators have noted that there may be an even higher efficacy of combination therapy with ipratropium and a β_2 agonist in the acutely ill patient, whereas others maintain that the severity of airflow obstruction does not affect the bronchodilator response. In Rebuck and associates' study of 148 acutely ill asthmatic patients,[161] those patients admitted to the emergency room with severe airflow obstruction, as demonstrated by a prebronchodilator $FEV_1 \leq 1$ L, responded with a more marked improvement to combination therapy than did those patients presenting with a baseline $FEV_1 > 1$ L. O'Driscoll and colleagues[169] also noted that those in greatest need respond with a higher degree of improvement to combination therapy utilizing ipratropium and a β_2 agonist. In this study, those patients with a peak expiratory flowrate < 140 L/min gained the maximum benefit from combined therapy. On the other hand, Higgins and associates[170] found no relationship between the degree of airway obstruction and the combined bronchodilator response in patients with acute severe asthma. The results of this study reveal that the β_2 agonist administered alone provided the maximum peak response. Although the overall maximal bronchodilator response did not improve with combination therapy, peak expiratory flowrates after 2 hours of administration were higher in the combined therapy group than those in the group treated only with salbutamol.

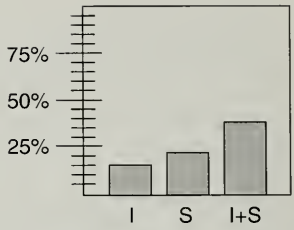
Comparative analysis of stable versus acute asthmatic patients receiving ipratropium in combination with a β_2 agonist suggests that both types of patients benefit from the greater efficacy and/or duration



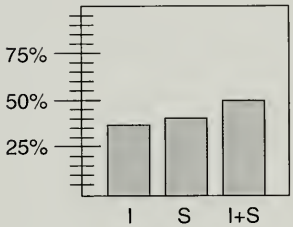
% change in mean FEV_1. Petrie & Palmer (1975);[155] double-blind, placebo-control; n = 8, stable asthma. Ipratropium = 0.04 mg; salbutamol = 0.2 mg.



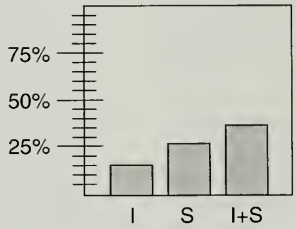
% predicted maximum increase in FEV_1. Bryant (1985);[156] double-blind; n = 28, acute asthma. Ipratropium = 0.5 mg; fenoterol = 1.0 mg.



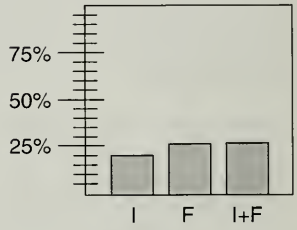
% change in mean FEV_1. Lightbody et al (1978);[157] single-blind, crossover; n = 11, stable asthma. Ipratropium = 0.04 mg; salbutamol = 0.2 mg.



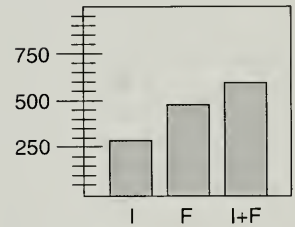
% change in mean PEFR. Ward et al (1981);[158] double-blind, crossover; n = 22, acute asthma. Ipratropium = 0.5 mg; salbutamol = 10 mg.



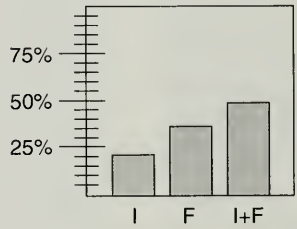
% change in mean PEFR. Leahy et al (1983);[159] uncontrolled; n = 12, acute asthma. Ipratropium = 1.0 mg; salbutamol = 5.0 mg.



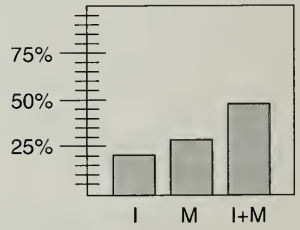
% change in mean FEV_1. Elwood & Abboud (1982);[160] double-blind, placebo-control; n = 10, stable asthma. Ipratropium = 0.04 mg; fenoterol = 0.2 mg; I (0.04 mg) + F (0.1 mg).



Increase in mean FEV_1 in mL. Rebuck et al (1983);[134] double-blind, placebo-control, crossover; n = 17, stable asthma. Ipratropium = 0.04 mg; fenoterol = 0.2 mg.

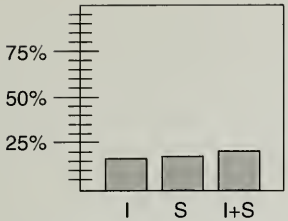


% change in mean FEV_1. Rebuck et al (1987);[161] double-blind; n = 148, acute asthma. Ipratropium = 0.5 mg; fenoterol = 1.25 mg.

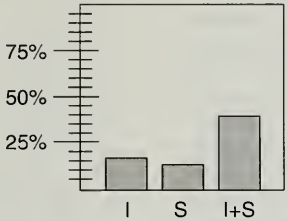


% change in mean FEV_1. Bruderman et al (1983);[162] double-blind, placebo-control; n = 10, stable asthma. Ipratropium = 0.04 mg; metaproterenol = 1.25 mg.

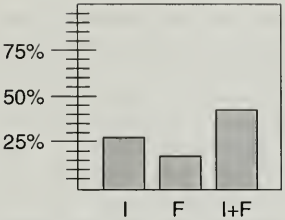
Fig. 3. Studies of comparative trials of aerosolized ipratropium bromide and a β_2-adrenoceptor agonist in patients with asthma.



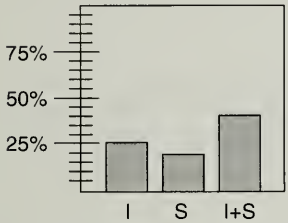
% change in mean FEV_1.Petrie & Palmer (1975);[155] double-blind, placebo-control; n = 8, stable bronchitis. Ipratropium = 0.04 mg; salbutamol = 0.2 mg.



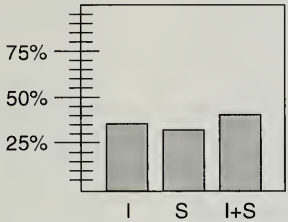
% change in mean FEV_1. Lightbody et al (1978);[157] single-blind, crossover; n = 10, stable bronchitis. Ipratropium = 0.04 mg; salbutamol = 0.2 mg.



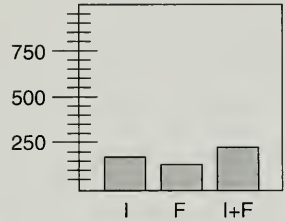
% change in mean FEV_1. Ferrer et al (1991);[163] double-blind, placebo-control; n = 24, stable COPD. Ipratropium = 0.5 mg; fenoterol = 5 mg.



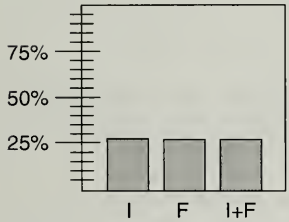
% change in mean FEV_1. Douglas et al (1979);[164] double-blind, placebo-control, crossover; n = 21, stable bronchitis. Ipratropium = 0.08 mg; salbutamol = 0.2 mg.



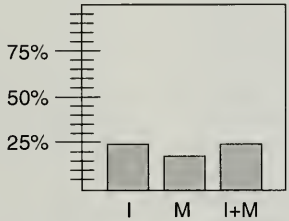
% change in mean PEFR. Howarth et al (1982);[165] uncontrolled; n = 12, stable COPD. Ipratropium = 1.0 mg; salbutamol = 5.0 mg.



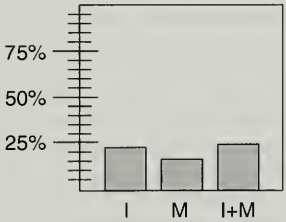
Increase in mean FEV_1 in mL. Hughes et al (1982);[166] double-blind, placebo-control, crossover; n = 12, stable emphysema. Ipratropium = 0.04 mg; fenoterol = 0.4 mg.



% change in mean FEV_1. Rebuck et al (1987);[161] double-blind; n = 51, acute COPD. Ipratropium = 0.5 mg; fenoterol = 1.25 mg.



% change in mean FEV_1. Karpel et al (1990);[167a] double-blind, crossover; n = 32, acute COPD. Ipratropium = 0.054 mg; metaproterenol = 1.95 mg.



% change in mean FEV_1. Karpel (1991);[167b] double-blind, placebo-control; n = 30, stable COPD. Ipratropium = 0.054 mg; metaproterenol = 1.95 mg.

Fig. 4. Studies of comparative trials of aerosolized ipratropium bromide and a β_2-adrenoceptor agonist in patients with COPD.

than that produced by either agent alone. The 9 studies listed in Figure 3 reveal that combined therapy exhibits a 41% (26-62% range) overall mean improvement above baseline. In addition, analysis of the positive additive-effect studies indicates that combination therapy has a mean improvement of 12% (6-18% range) over the singly administered β_2 agent. While Petrie and Palmer's[155] and Elwood and Abboud's[160] subjects did not exhibit higher peak responses with combination therapy, a longer duration of activity resulted from the combined regimen. Elwood and Abboud[160] compared the low-to-high dosage ranges of fenoterol and ipratropium; a combined dose of 0.1-mg fenoterol plus 0.04 mg of ipratropium produces bronchodilation equivalent in extent but without the side effects of a 0.2-mg dose of fenoterol. Therefore, lower doses of each agent, when given in combination, could offer similar efficacy with reduced or minimal side effects.

Three methods were utilized in administering the combination therapy to patients: (1) ipratropium and the β_2 agonist were administered simultaneously, or (2) ipratropium was given prior to the β_2 agonist, or (3) the β_2 agonist was given prior to ipratropium. Most of the investigators used only 1 of the 3 methods, whereas a few investigators did use both Methods 2 and 3 to determine if there was a treatment order difference. The majority of investigators who used both Methods 2 and 3 in their studies indicate that the most effective method is Method 2 in which ipratropium is given before the β_2 agonist.[158,159,162,171] In these clinical trials, a significant additive and more prolonged effect resulted when ipratropium was given prior to the β_2 agonist. When the order of administration was reversed, the positive additive effect was either not as great or was not present. The study by Leahy and colleagues[159] of 12 acutely ill asthmatic patients confirms how important correct sequencing can be; in that study, when the β_2 agonist was administered after ipratropium, a further mean increase in respiratory function of 20% resulted, compared with a mean increase of only 6% when ipratropium followed the β_2 agonist (Fig. 5). In addition, the combination resulted in a longer duration of effectiveness when ipratropium was given first. Bruderman and associates' study[162] of 10 stable asthmatics realized similar gains in the effectiveness and duration of activity when ipratropium was given first. However, unlike the results

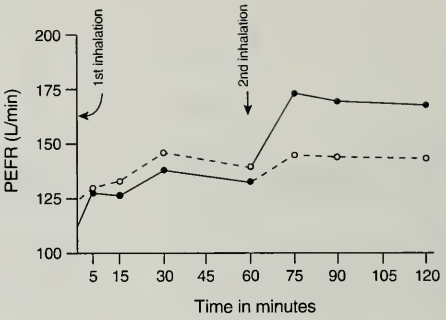


Fig. 5. Comparative effects of sequencing ipratopium bromide (○--○) with a β_2-adrenoceptor agonist (●—●). A higher efficacy is achieved when the β_2-adrenoceptor agonist follows ipratropium. (Based on data from Reference 159.)

in the Leahy et al study, by reversing the order of drugs, with metaproterenol administered prior to ipratropium, an additive effect could not be produced (Fig. 6).

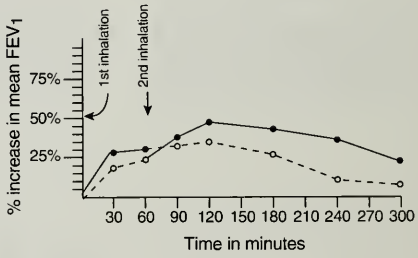


Fig. 6. Comparative effects of sequencing ipratropium bromide (○--○) with a β_2-adrenoceptor agonist (●—●). The most effective combination is achieved when ipratropium is administered prior to the β_2 agonist. (Based on data from Reference 162.)

The possible explanation for the higher efficacy and sustained response that is generated when ipratropium is administered prior to the β_2 agonist is based on two primary postulates:[20,21,26,27,70,71,162,172,173] (1) inhaled ipratropium dilates larger airways predominantly, whereas inhaled β_2 agonists dilate the smaller, peripheral airways (hence, a more favorable deposition into the peripheral airways results if the β_2 agonist is given as a second inhalation); and (2) in those subjects

who tend to have increased vagal tone, the additive effect of a β_2 agonist may be obtained only when vagal tone is decreased. Antimuscarinic agents inhibit vagal efferent pathways and, therefore, can significantly counteract increased vagal influences. Once this vagal influence is negated by administration of an antimuscarinic, the β_2 agonist may be able to elicit more effective results. On the basis of these studies, it seems that correct sequential administration of drugs of the two types plays a vital role in enhancing the effectiveness and duration of activity.

The majority of published trials indicate that an additive effect is achieved when ipratropium and a β_2 agonist are given in combination to the asthmatic patient. In addition to the clinical trials listed in Figure 3, several other investigators have found a positive additive effect when ipratropium is administered in combination with a β_2 agonist.[97,169,171,174-184] However, some clinical trials, in addition to those listed in Figure 3, have found that a β_2 agonist administered alone achieves the maximal response or that combination therapy elicits a nonsignificant, slightly higher efficacy.[170,185-188] Yet, in some of these studies, a sustained duration was noted with combination therapy, which may be a clinically useful effect.[155,160,170,185]

The data from the clinical trials comparing the efficacy of atropine sulfate or atropine methonitrate and a β_2 agonist support these findings in that the β_2 agonist is a superior bronchodilator over atropine in the asthmatic patient.[24,189-196] Several investigators have found that combination therapy with atropine and a β_2 agonist elicits a significantly different degree of response, according to the type of patient being studied. Atropine in combination with a β_2 agonist in stable asthmatics generally produced significantly greater and more lasting bronchodilation;[35,36,189-191,197] whereas in acutely ill patients with more severe airway obstruction, response was poor (ie, effects were not additive) and more side effects were seen.[193-196] Results in these studies contrast with the clinical trials of ipratropium in which combination therapy was usually beneficial and additive in both stable and acutely ill patients. Possible reasons for the conflicting reports may be that, as mentioned previously, ipratropium is a more effective bronchodilator at recommended doses and has few or no side effects, whereas atropine's primary dose-limiting factor is its systemic side effects.

Analysis of Comparative Trials of Patients with Chronic Obstructive Pulmonary Disease (COPD)

Patients with an asthmatic component to their disease (defined as reversibility with β_2 agonists) often have been excluded from bronchodilator response studies conducted on COPD patients.[37,48,53,163,167a,167b,198] Yet the complete exclusion of these 'overlap' patients is often arbitrary and difficult. Therefore, variable results may occur in some clinical trials because of the inadvertent inclusion of some patients with asthma. If the asthmatic component were truly factored out, it would then be expected that cholinergic tone would predominate as the reversible component of airway obstruction in COPD patients;[198] and, as a result, antimuscarinic agents would prove to be the superior bronchodilators in such patients. The reader is encouraged to review the reports of these studies to specifically delineate the type of patient population being tested (Fig. 4[155,157,161,163-167]).

An overview of this group of studies suggests that the antimuscarinic agent, ipratropium, is indeed slightly more efficacious (with mean improvement 25%, range 15-35%, above pretreatment baseline FEV_1 or PEFR) than the β_2 agonist (with mean improvement 20%, range 13-33% above baseline), in patients with COPD. The differences in effectiveness between the two groups of drugs is not statistically significant as it is in the asthmatic patients. The finding in the group of emphysema patients was that the antimuscarinic agent significantly increased the vital capacity rather than increasing flow measurements. Hughes and colleagues[166] suggest that this finding is associated with a reduced functional residual capacity due to the decrease in bronchomotor tone resulting from cholinergic blockade. In the emphysema patients, ipratropium attained maximum effect at least as rapidly as the β_2 agonist.[199,200]

Worthy of mention is the clinical trial with stable COPD patients by Tashkin and colleagues.[48] Although this study was not included in Figure 4 because the investigators did not administer combination therapy, it has a three-fold significance: (1) it was a 90-day multicenter study of 261 patients, (2) the study was carefully constructed to include only patients with clearly defined COPD, and (3) it clearly established that ipratropium produces a signifi-

cantly greater and longer (up to 6 hours) response in COPD patients than does a β_2 agonist. Of interest also is that ipratropium maintained this heightened response and increased duration of bronchodilation over the β_2 agonist for the entire 90-day trial period. Figure 7 summarizes the overall results on 3 separate occasions during this study: Day 1, Day 45, and Day 90. Several other studies,[42,182,184,188,199-204] in addition to those listed in Figure 4, agree with the results noted by Tashkin and colleagues in that a greater magnitude of response and/or duration of effectiveness was achieved with ipratropium over a β_2 agonist in the COPD patient.

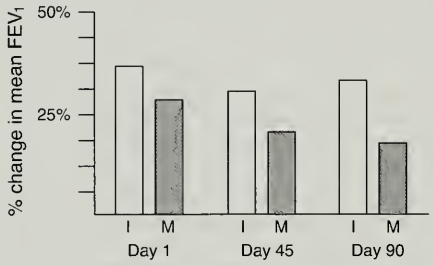


Fig. 7. Comparative response between ipratropium bromide (I) and metaproterenol (M) in patients with COPD. (Based on data from Reference 48.)

Analysis of the combination therapy in these 9 studies discloses a mean improvement rate over all of 32% (range 20-41%). Six studies reveal a positive additive effect with a mean increase of 12% (range 5-22%) over the antimuscarinic agent administered alone. It is interesting that Lightbody and colleagues[157] found evidence for summation of improvement when ipratropium and albuterol were administered together. As was found in the asthmatic patients, combination therapy in patients with bronchitis-emphysema resulted in a relatively longer duration of bronchodilation than what either agent could provide alone. The clinical trial conducted by Howarth and associates[165] noted that the peak expiratory flowrate was still 25.5% above baseline 7 hours after aerosols of the two drug types were administered together.

A 1991 clinical trial conducted on COPD patients with acute exacerbations indicated that, on the average, those patients who received combination therapy with ipratropium and a β_2 agonist were discharged from the emergency department 91 minutes sooner than the control group who received only a β_2 agonist. Further, the patients who received combination therapy averaged one less β_2-agonist treatment than the control group.[205]

The absence of a positive additive effect is noticeable in three studies listed in Figure 4.[161,167a,167b] These studies suggest that either ipratropium or the β_2 agonist alone produced the greatest possible response, and no additional improvement could be achieved with inhalation of the other drug. In Karpel's study of acutely ill and stable COPD patients,[167a,167b] ipratropium was the mediator of maximal response. However, the differences between peak response with ipratropium and metaproterenol were not significant. The study by Rebuck and associates[161] indicates that both aerosols are equipotent in eliciting a maximal response and the addition of a second agent is of no practical value. The study of COPD patients by Easton and associates[206] found that the β_2 agonist produced the highest peak response and only a small, nonsignificant gain was noted with combination therapy. Unfortunately, the studies of Karpel, Rebuck, and Easton measured peak responses for only 180 minutes, 90 minutes, and 150 minutes, respectively. Whether the combined therapy would have produced a more sustained response is not known.

The comparative response study by Karpel and associates is a two-phase report: The first phase studied COPD patients when in acute exacerbations,[167a] whereas the second phase studied those same patients when they were stable.[167b] Although the FEV_1 was significantly improved in the second phase of the study when the patients were stable, the results of both phases of treatment indicate that the differences in peak response to either ipratropium or metaproterenol do not differ (reported in Fig. 4). Contrary to the Karpel study is the study conducted by Braun and colleagues[204] that shows that bronchial responsiveness to ipratropium is heightened in proportion to the severity of airway disease. Twenty-five patients with moderate-to-severe chronic bronchitis (mean FEV_1 34% of predicted) participated in this study. Ipratropium (36 μg), albuterol (200 μg), or placebo was administered in a random fashion. Not only was the improvement in respiratory function significant after the administration of

ipratropium but also duration of bronchodilation was greater than with albuterol. In addition, those subjects with a lower prebronchodilator FEV_1 and a greater pack-year smoking history responded to ipratropium with a more marked improvement.

Several comparative response trials with atropine sulfate or atropine methonitrate and a β_2 agonist in patients with COPD indicate that atropine is as effective[24,207,208] and frequently more effective than the β_2 agonist.[23,37,198,209] Some investigators found that those patients with moderate-to-severe airways obstruction achieved a higher peak response to atropine than did those with less severe obstruction.[198]

PRECIPITATORS OF BRONCHOSPASM

The importance of the data presented in Figures 3 and 4 can be clarified when one reviews the precipitators of bronchospasm in patients with airflow obstruction. Structural narrowing, loss of elastic recoil, and fibrotic distortion, combined with a degree of vagal bronchomotor tone, are seen in the airways of patients with chronic obstructive pulmonary disease. Loss of elastic recoil and fibrotic distortion are irreversible, whereas other components of airway obstruction in patients with COPD are potentially reversible—mucus obstruction, airway inflammation, and bronchial smooth muscle contraction.[37,198,210] Although patients with COPD generally do not have a significant reversible component to their airway obstruction, many patients in this group exhibit at least a 10-20% improvement in their flowrates as seen in Figure 4. As also can be noted in Figure 4, the antimuscarinic agent ipratropium bromide produced equivalent and, in some cases, greater bronchodilation than the β_2 agent. Many investigators believe that vagal tone is the major reversible element of this disorder and conclude that an antimuscarinic agent should be first-line therapy.[23,28,37,198,210]

The airways of asthmatic patients are hyperresponsive to a multitude of precipitators of bronchospasm. Mast cell degranulation with the resultant release of histamine and the formation of other endogenous mediators of inflammation (serotonin, bradykinin, prostaglandins, and leukotrienes) play a role in regulating airway caliber in these patients.[13,61,66,67,211] β_2 agents are considered first-line therapy against the effects of these types of inflammatory mediators.[66,67,212-214] Antimuscarinic agents are relatively ineffective or, at most, provide limited protection against bronchospasm induced by histamine, bradykinin, serotonin, or prostaglandin $F_{2\alpha}$.[213-217]

β_2 agents are also considered first-line therapy for exercise-induced and cold-air-induced bronchospasm and for allergens and exogenous irritants.[189,212,218-221] However, in some asthmatics, ipratropium and atropine effectively reduce the severity of exercise- and cold-air-induced bronchospasm when given prior to exercise or exposure to cold air.[25,189,215,222-224] Some investigators suggest that combination therapy may provide more protection for patients with moderate-to-severe exercise-induced asthma,[189,224] whereas others maintain that if effective control is not obtained with conventional doses of antimuscarinics, larger doses may be effective.[225] McFadden and associates[25] found that either of two airway sites are affected by the bronchoconstriction brought on by exercise. Of the 12 asthmatic patients tested, 5 had predominantly large-airway obstruction after exercise, whereas the other 7 had predominantly small-airway obstruction after exercise. In the large-airway-obstruction group, antimuscarinic therapy totally abolished the bronchospastic response to exercise, whereas antimuscarinic therapy in the small-airway-obstruction group was relatively ineffective in altering the response to exercise.

The experimental findings of several investigators indicate that antimuscarinics reliably protect against cholinergically mediated (acetylcholine, methacholine) bronchospasm and bronchospasm induced by certain irritants such as house dust, grass pollen, molds, animal hair, cigarette smoke, ozone, and citric acid.[213,215-217,226] Some studies also indicate that patients whose asthma is brought on by psychogenic factors respond more favorably to antimuscarinic therapy than to β_2 agonist therapy.[227-229]

ß-blocking agents can precipitate severe bronchospasm in asthmatic patients by blocking ß-adrenergic opposition to parasympathetic tone.[230-232] Antimuscarinic agents provide a moderate degree of protection by preventing and reversing such bron-

chospasm, whereas the β_2 agonists are less effective.[216,231-233]

Ullah and associates[176] found that asthmatics 40 years of age or younger responded better to the β_2 agonist than to the antimuscarinic agent, whereas asthmatics older than 40 years responded better to the antimuscarinic agent. The authors conclude that β-adrenergic responsiveness declines with age. However, the clinical trial conducted by Kradjan and colleagues[234] found albuterol and ipratropium effective bronchodilators in both young and older asthmatics. Although albuterol resulted in a higher peak response, the response was of the same magnitude in both age groups. The authors concluded that β-adrenergic responsiveness does not decline with age. Table 3 lists precipitators of bronchospasm with the bronchodilator found to be most effective in reversing the obstruction.

SUMMARY

β_2-adrenergic agonists and antimuscarinic agents are both highly effective bronchodilators in the treatment of reversible airway obstruction. On the basis of the available evidence, β_2 agonists have greater efficacy in the treatment of asthma, whereas COPD patients generally benefit more from antimuscarinic agents. For the management of acute bronchospasm, the β_2 agonist is preferred because of its rapid onset of action.

Many of the studies presented re-emphasize the heterogeneity of airway responses to all stimuli and suggest that prophylaxis be directed at peripheral as well as large central airways. In many patients with airflow obstruction, the use of an antimuscarinic with a β_2 agonist increases the efficacy and duration of response and/or lowers the incidence of side effects. The additional bronchodilation achieved by combination therapy may be related to differences in the pharmacologic properties of each drug type or to differences in receptor sites within the airways. Because of these differences in action, the effects of the two drugs may be additive.

When combination therapy is used, the sequence of administration may affect the response. In many cases, a greater efficacy and more prolonged effect is achieved when the antimuscarinic agent is administered prior to the β_2 agonist.

Table 3. Summary of Precipitators of Bronchospasm and Efficacy of Inhaled Bronchodilators

Bronchoconstricting Stimulus	Antimuscarinic Agents	β_2-Adrenoceptor Agents
Asthma:		
Cholinergic agents (acetylcholine, methacholine)	Fully effective	Less effective
Beta-blockers	Effective reversal	Less effective
Allergens-irritants	Moderately effective (studies vary from none to excellent)	Very effective
Exercise-induced, cold air	Moderately effective (more so in large doses or if given prior to exercise)	Very effective
Various mediators (histamine, serotonin, bradykinin, prostaglandin $F_{2\alpha}$)	Limited effectiveness (partially protective at most)	Moderate to very effective
Emotional (psychogenic) factors	Very effective	Less effective
Chronic Obstructive Disease:		
Bronchitis	Moderately effective	Moderately effective
Emphysema	Moderately effective	Less effective

Whatever bronchodilator regimen is chosen for the patient, optimal therapy can be defined as maximum efficacy with minimal adverse effects. In all situations, it must be remembered that patients are individuals and require a regimen tailored to their individual needs.

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accp consensus conference

Mechanical Ventilation*

Chairman: Arthur S. Slutsky, M.D., F.C.C.P.

(Chest 1993; 104:1833-59)

A/C = assist-control ventilation; APRV = airway pressure release ventilation; ARDS = adult (or acute) respiratory distress syndrome; auto-PEEP = increase (above set PEEP level) in end-exhalation alveolar pressure (also termed dynamic hyperinflation, intrinsic PEEP, also quantified as $\dot{V}_{EE}$); BPF = bronchopleural fistula; C_{aO_2} = content of oxygen in arterial blood; CMV = conventional mechanical ventilation; CPAP = continuous positive airway pressure; DH = dynamic hyperinflation (see auto-PEEP); $\dot{D}_{O_2}$ = oxygen delivery; ECMO = extracorporeal membrane oxygenation; $ECCO_2R$ = extracorporeal CO_2 removal; ET = endotracheal; F_{IO_2} = fractional concentration of inspired oxygen; FRC = functional residual capacity; HFJV = high-frequency jet ventilation; HFV = high-frequency ventilation; ICP = intracranial pressure; I:E = inspiratory-expiratory ratio; ILV = independent lung ventilation; IMV = intermittent mandatory ventilation; IRV = inverse ratio ventilation; IVOX = intravascular blood gas exchanger; LFPPV = low frequency positive pressure ventilation; LV = left ventricle; MalvP = mean alveolar pressure; MAP = mean airway pressure; MMV = mandatory minute ventilation; OAD = obstructive airways disease; PAP = peak airway pressure, pulmonary artery pressure; Paw = airway pressure; PCIRV = pressure-controlled inverse ratio ventilation; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; Pmus = pressure generated by muscle contraction; Ppl = pleural pressure; PPV = positive pressure ventilation; PS = pressure support; PSV = pressure support ventilation; Ptot = total distending pressure; P-V = pressure-volume; RA = right atrium; RV = right ventricle, residual volume; S_{aO_2} = oxygen percent saturation (arterial); SIMV = synchronized intermittent mandatory ventilation; T_I = inspiratory time; TLC = total lung capacity; VC = vital capacity; $\dot{V}_{CO_2}$ = CO_2 production (elimination); V_D = dead space; $\dot{V}_E$ = minute ventilation; $\dot{V}_{EE}$ = end-expiratory lung volume; $\dot{V}_{EI}$ = end-inspiratory lung volume; $\dot{V}/\dot{Q}$ = ventilation/perfusion ratio; V_T = tidal volume; $\dot{V}_{O_2}$ = oxygen consumption (uptake).

"But that life may ... be restored to the animal, an opening must be attempted in the trunk of the trachea, in which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and the animal take in air. ... And as I do this, and take care that the lung is inflated in intervals, the motion of the heart and arteries does not stop ..."[1]

Andreas Wesele Vesalius, 1543

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Objectives and Specific Recommendations

Section 1: Objectives of Consensus Committee

Although the concept of artificial respiration was recognized in the 16th century by Vesalius, it was not until the 20th century that mechanical ventilation became a widely used therapeutic modality. Over the past 30 years, and especially over the past decade, there has been an explosion of new ventilatory techniques that present a bewildering array of alternatives for the treatment of patients with respiratory failure. Unfortunately, although the number of options available to the clinician has appeared to increase exponentially, well-controlled clinical trials defining the specific role for each of these modes of ventilation and comparing them to other modes of ventilation have not been forthcoming. In addition, over the past few years our understanding of the detrimental as well as beneficial effects of mechanical ventilation has increased, along with novel strategies for limiting these negative effects.

These issues formed the impetus for the consensus conference described in this document; the conference was held in Chicago on January 28-30, 1993. The consensus committee was international in scope (Europe, North America, New Zealand) and consisted of individuals from a broad range of backgrounds (anesthesia, critical care, pulmonary, respiratory therapy). The purpose of the conference was to summarize key concepts related to mechanical ventilation and to present recommendations based on these concepts for clinicians applying mechanical ventilation in the adult ICU setting. Due to the lack of randomized clinical studies on most aspects of ventilatory care, the underlying theme of this document is a physiologic one, the basic tenet being that if the clinician understands the physiologic principles, he or she can apply mechanical ventilation at the bedside in a rational manner. We recognize that rational application of mechanical ventilation does not, in and of itself, guarantee the therapy will be beneficial to the patient. We await randomized clinical-trial results for ultimate guidance.

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The purpose of the consensus conference was not to deal with every possible aspect of mechanical ventilation. Rather, the focus was on treatment of patients with acute ventilatory failure and the principles of ventilation *after* the decision to initiate mechanical ventilation has been made. The technical needs and medical issues of ventilatory support in non-ICU settings were not dealt with specifically by this conference. These issues include ventilatory support during anesthesia and surgery; patient treatment during intrahospital, land, or air transport; and long-term mechanical ventilation in the home. Also not covered were noninvasive (nonintubated) ventilatory support, negative pressure ventilation, and methods and devices for respiratory support not primarily applied to the lungs, such as extracorporeal membrane oxygenation (ECMO), extracorporeal carbon dioxide removal ($ECCO_2R$), or intravascular blood gas exchanger (IVOX). This conference focused on the clinical application of mechanical ventilators, rather than on their design and operation. Thus, the participants consider these proceedings to be complementary to those of the 1992 AARC Consensus Conference on the Essentials of Mechanical Ventilators.[2]

Despite the multidisciplinary and international composition of the conference, we were able to reach agreement on many difficult clinical issues. Yet even though we engaged in considerable discussion and debate, consensus was not possible on a number of aspects of ventilator care. This is hardly surprising and merely reflects the variety of acceptable approaches that can be used to treat patients with respiratory failure. For example, it was not possible to agree that there was an optimum *mode* of ventilation for any disease state or an optimum method of weaning patients from mechanical ventilation. However, in addition to the specific recommendations discussed in Section 2, there was general agreement on the following principles that should guide the use of mechanical ventilation:

1. The underlying pathophysiology of various disease states varies with time, and thus the mode, settings, and intensity of ventilation should be reassessed repeatedly.

2. Mechanical ventilation is associated with a number of adverse consequences, and, as such, measures to minimize such complications should be implemented wherever possible.

3. To minimize side effects, the physiologic targets do not have to be in the normal range. For example, at times it may be beneficial to allow the P_{aCO_2} to increase (controlled hypoventilation, permissive hypercapnia) rather than risk the dangers of lung hyperinflation.

4. Alveolar overdistention can cause alveolar damage or air leaks (barotrauma). Hence, maneuvers to prevent the development of excess alveolar (or transpulmonary) pressure should be instituted if necessary. While recognizing that the causes of ventilator-induced lung injury are multifactorial, the consensus committee generally believed that end-inspiratory occlusion pressure (*ie*, plateau pressure) was the best, clinically applicable estimate of average peak alveolar pressure, and, thus, was the most important target pressure when trying to avoid alveolar overdistention. Many individuals on the consensus committee believed that high plateau pressures (>35 cm H_2O) may be more harmful in most patients than high values of F_{IO_2}.

5. Dynamic hyperinflation (DH) (gas trapping, auto-PEEP, intrinsic PEEP) often goes unnoticed and should be measured or estimated, especially in patients with airway obstruction. Management should be directed toward limiting the development of DH and its adverse consequences in these patients.

This consensus document is divided into two major sections: part 1 summarizes the objectives and specific recommendations of the consensus committee; part 2 reviews key principles regarding physiology, complications, and modes of ventilation that form the basis for the recommendations.

Section 2: Objectives of Mechanical Ventilation

Mechanical ventilation and continuous positive airway pressure (CPAP) are methods of supporting intubated patients during illness, and are not, in and of themselves, curative or therapeutic. Indeed, in certain clinical settings, there may be effective alternative therapies that do not require intubation and mechanical ventilation. The fundamental objectives for ventilatory support in acutely ill patients may be viewed physiologically and clinically, as detailed below. The following objectives should be kept in mind, not only when mechanical ventilation is initiated, but also at frequent intervals during the period of support; mechanical ventilation should be withdrawn whenever the underlying pathophysiologic rationale for initiating mechanical ventilation is no longer present.

A. Physiologic Objectives

1. To Support or Otherwise Manipulate Pulmonary Gas Exchange:

(i) Alveolar Ventilation (eg, Arterial P_{CO_2} and pH).

In most applications of ventilatory support, the objective is to normalize alveolar ventilation. In certain specific clinical circumstances, the objective may be to achieve an alveolar ventilation greater than normal (as in deliberate hyperventilation to reduce intracranial pressure [ICP]), or adequate but less than normal (as in permissive hypercapnia or acute-on-chronic ventilatory failure).

(ii) Arterial Oxygenation (eg, P_{aO_2}, S_{aO_2}, and C_{aO_2}).

A critical objective of mechanical ventilation is to achieve and maintain a level of arterial blood oxygenation that is acceptable for the clinical setting, using an inspired oxygen concentration that is also acceptable. In most applications of ventilatory support, this means an $S_{aO_2} > 90\%$ (roughly equivalent to a $P_{aO_2} > 60$ mm Hg assuming a normal position of the oxyhemoglobin dissociation curve), although other end points are appropriate in certain settings. There is no clinical evidence that a P_{aO_2} greater than

normal is advantageous. Given other techniques for improving oxygenation, this objective would seldom be the only reason for initiating mechanical ventilation. Because arterial oxygen content is determined by hemoglobin as well as P_{aO_2}, and because systemic oxygen delivery is directly related to cardiac output (Q_t), as well as content of oxygen in arterial blood (C_{aO_2}), these factors must also be considered in therapy aimed at improving tissue oxygenation.

2. To Increase Lung Volume:

(i) End Inspiratory Lung Inflation.

To achieve sufficient lung expansion, with every breath (or intermittently), to prevent or treat atelectasis and its attendant effects on oxygenation, compliance, and lung defense mechanisms.

(ii) Functional Residual Capacity (FRC).

To achieve and maintain an increased FRC using PEEP in settings in which a reduction in FRC may be detrimental (*eg*, decreased P_{aO_2}, increased lung injury) as in ARDS and postoperative pain.

3. To Reduce or Otherwise Manipulate the Work of Breathing:

(i) To Unload the Ventilatory Muscles.

To reduce the patient's work of breathing when it is increased by elevated airway resistance or reduced compliance and the patient's spontaneous efforts are ineffective or incapable of being sustained. In these situations, ventilatory support will be used until specific therapies (or other mechanisms) reverse the condition leading to the increased work load.

B. Clinical Objectives

Because, at best, mechanical ventilation serves only to support the failing respiratory system until improvement in its function can occur (either spontaneously or as a result of other interventions), a primary objective should be to avoid iatrogenic lung injury and other complications.

The other primary clinical objectives of mechanical ventilation are as follows:

1. *To Reverse Hypoxemia:* To increase P_{aO_2} (generally such that $S_{aO_2} \geq 90$ percent), whether through increasing alveolar ventilation, increasing lung volume, decreasing O_2 consumption, or other measures, to relieve potentially life- or tissue-threatening hypoxia.

2. *To Reverse Acute Respiratory Acidosis:* To correct an immediately "life-threatening" acidemia, rather than necessarily to achieve a normal arterial P_{CO_2}.

3. *To Relieve Respiratory Distress:* To relieve intolerable patient discomfort while the primary disease process reverses or improves.

There are well-defined circumstances in which attempts to improve P_{aO_2} or pH to their normal ranges would present greater overall risks to the patient, and lower values of these parameters may be appropriate in such circumstances. In addition to the main clinical objectives listed above, other specific goals for mechanical ventilation, in appropriate settings, include the following:

4. *To Prevent or Reverse Atelectasis:* To avoid or correct the adverse clinical effects of incomplete lung inflation, as, for example, in postoperative splinting or neuromuscular disease.

5. *To Reverse Ventilatory Muscle Fatigue:* In most instances, this means unloading the ventilatory muscles in circumstances of acutely increased and intolerable loads.

6. *To Permit Sedation and/or Neuromuscular Blockade:* To allow the patient to be rendered incapable of spontaneous ventilation, as for operative anesthesia and certain ICU procedures and in certain disease states.

7. *To Decrease Systemic or Myocardial Oxygen Consumption:* To lower systemic and/or myocardial oxygen consumption ($\dot{V}_{O_2}$) when the work of breathing or other muscular activity impairs systemic O_2 delivery or produces an overload of the compromised heart. Examples include cardiogenic shock or severe ARDS.

8. *To Reduce Intracranial Pressure (ICP):* In certain circumstances (*eg*, acute closed head injury), to lower elevated ICP through controlled hyperventilation.

9. *To Stabilize the Chest Wall:* In the unusual circumstance of loss of thoracic integrity sufficient to prevent adequate bellows function (*eg*, chest wall resection, massive flail chest), to provide adequate ventilation and lung expansion.

Section 3: Clinical Recommendations

A. Mechanical Ventilation for Specific Entities

Adult Respiratory Distress Syndrome (ARDS): Although it has been argued that patients with ARDS are now more severely ill than those encountered in the past, the failure of ARDS mortality to decrease during the past 15 to 20 years is disappointing, particularly in light of the many technical advances in ICU care. Criteria that selected a severely hypoxemic subset of patients with ARDS were established in the 1974 to 1977 ECMO clinical trial. Recent work indicates that the average survival of such patients with severe ARDS treated with conventional mechanical ventilation only ranges from 0 percent to 15 percent (mean = 12.8 ± 5.2 percent).[3] This is not statistically significantly different from the ECMO clinical trial survival of 9 percent ($p = 0.15$). Recent changes in ventilatory management may have led to increased patient survival, but to our knowledge, this has not been evaluated with controlled clinical trials.[4-6]

There are no convincing data indicating that any ventilatory support mode is superior to others for patients with ARDS. Nevertheless, reported increases in ARDS patient survival have been ascribed to new techniques such as pressure-controlled inverse ratio ventilation (PCIRV) and low-frequency positive pressure ventilation-extracorporeal

CO_2 removal (LFPPV-ECCO$_2$R). If they are harbingers of new and effective therapy, their putative benefit may be linked to current concern about iatrogenic lung damage induced by mechanical ventilation. Animal studies have clearly established the damaging effects of overdistention produced by the application of high peak transthoracic pressures to normal and injured lungs. In humans, the nonuniformly injured severe ARDS lung retains only a small fraction of compliant lung still capable of gas exchange. It has been argued that the application of commonly used tidal volumes (0.7 L, 10 ml/kg) to this small fraction of lung may produce similar damage.[3] The best correlate of this injury in animals is the plateau pressure. Conventional mechanical ventilator (CMV) therapy might thus superimpose iatrogenic lung injury. The "lung rest" strategy used in neonatal ECMO therapy,[7] intentional hypoventilation used in patients with ARDS,[4] and reduction of peak pressures permitted by PCIRV or by LFPPV-ECCO$_2$R[8] are consistent with this argument. There is, however, no proof that any of these techniques alter the outcome of patients with ARDS. A recent randomized controlled clinical trial of PCIRV plus LFPPV-ECCO$_2$R failed to produce evidence of improved survival.[9] Of interest is the fourfold increase in survival of control patients treated with mechanical ventilation only, according to a computerized protocol.[9]

Guidelines:

1. The clinician should choose a ventilator mode that has been shown to be capable of supporting oxygenation and ventilation in patients with ARDS and that the clinician has experience in using.

2. An acceptable S_{aO_2} (usually ≥90 percent) should be targeted.

3. Based primarily on animal data, a plateau pressure ≥35 cm H_2O is of concern. We, therefore, recommend that when plateau pressure equals or exceeds this pressure that tidal volume (V_T) can be decreased (to as low as 5 ml/kg, or lower, if necessary). With clinical conditions that are associated with decreased chest wall compliance, plateau pressures somewhat greater than 35 cm H_2O may be acceptable.

4. To accomplish the goal of limiting plateau pressure, P_{aCO_2} should be permitted to rise (permissive hypercapnia) unless the presence or risk of raised ICP or other contraindications exist that demand a more normal P_{aCO_2} or pH. Rapid rises in P_{aCO_2} should be avoided. In the presence of normal renal function, slow reduction of tidal volume may also allow renal-induced compensatory metabolic alkalosis and the potential for a higher pH at a given tidal volume.

5. Positive end-expiratory pressure (PEEP) is useful in supporting oxygenation. An appropriate level of PEEP may be helpful in preventing lung damage. The level of PEEP, however, should be minimized as PEEP may also be associated with deleterious effects. The level of PEEP required should be established by empirical trial and reevaluated on a regular basis.

6. The current opinion is that F_{IO_2} should be minimized. The trade-off, however, may be a higher plateau pressure and the relative risks of these two factors are not known. In some clinical situations when significant concerns over both elevated plateau pressure and high F_{IO_2} exist, consideration for accepting an S_{aO_2} slightly less than 90 percent is reasonable.

7. When oxygenation is inadequate, sedation, paralysis, and position change are possible therapeutic measures. Other factors in oxygen delivery (*ie*, $\dot{Q}_t$ and hemoglobin) should also be considered.

Bronchopleural Fistula: Bronchopleural air leak (bronchopleural fistula [BPF]) occurs during mechanical ventilation in two general circumstances: as a localized lung or airway lesion (*eg*, following trauma or surgery; complicating central line placement) and as a complication of diffuse lung disease (*eg*, ARDS, *Pneumocystis carinii* pneumonia). Although most leaks are physiologically insignificant, BPF can predispose to atelectasis or inadequate inflation of ipsilateral or contralateral lung, interfere with gas exchange, and predispose to pleural spread of infection. It can also prolong mechanical ventilation thus predisposing to additional morbidity. Some BPFs are amenable to direct surgical repair (*eg*, suture of bronchial tear; lobectomy for necrotizing pneumonia), but in most instances, resolution of the BPF depends on resolution of the primary disease process.

Ventilatory support should provide adequate inflation for the uninvolved areas of lung and assure adequate gas exchange.[10] No single ventilatory mode or approach has been shown to be more effective than any other in treating patients with BPF. In the presence of a large air leak and difficulty in maintaining adequate ventilation, a ventilator capable of delivering high inspiratory flow rates and large delivered tidal volumes may be required. Use of independent lung ventilation (ILV) should be considered in the uncommon circumstance of inability to maintain contralateral lung inflation using adjustments of volumes and/or flows. Fortunately, ventilation of patients with BPF is usually adequate. The major problem is usually to facilitate closure of the leak, so that mechanical ventilator support may be withdrawn. In this circumstance, minimizing inflation pressures and tidal volume is the goal. Chest tube suction is necessary to evacuate continued gas leak, but the degree of suction exerts a variable effect on flow through the fistula.[11]

Guidelines:

1. To facilitate closure.

a. Use the lowest tidal volume that allows adequate ventilation.

b. Use a ventilatory mode and settings that minimize peak and plateau pressures necessary to maintain adequate ventilation.

c. Consider permissive hypercapnia (discussed under guidelines 3 and 4 under ARDS) to minimize inspiratory pressures and volumes.

d. Minimize PEEP.

2. Consider independent lung ventilation (ILV) or high frequency jet ventilation (HFJV) in cases where a large air leak produces inability to inflate lung or failure to adequately oxygenate/ventilate.

Head Trauma: Mechanical hyperventilation to arterial carbon dioxide levels of 25 to 30 mm Hg acutely lowers ICP. Controlled data on the impact of hyperventilation in patients with head trauma are not available. Decreases in ICP do not necessarily reflect increases in cerebral perfusion pressure. Nevertheless, hyperventilation remains a mainstay of emergency therapy for acutely elevated ICP. There is no evidence to support the application of prophylactic hyperventilation in patients with head injury who do not have raised ICP.[12,13] In fact, there is a strong rationale for maintenance of normocarbia in most head-injured patients without elevated ICP because a patient who has prophylactically been hyperventilated to a P_{aCO_2} in the high 20s and who suffers an acute increase in ICP may not be expected to have an effective reduction in ICP following a moderate increase in minute ventilation ($\dot{V}_E$). Since the patient is already hyperventilated, a marked increase in $\dot{V}_E$ may be required to effect a significant lowering of P_{aCO_2}. The increase in mean airway pressure associated with a dramatic increase in $\dot{V}_E$ may cause a paradoxic increase in ICP. Therefore, it is likely that stable head-injured patients should receive mechanical ventilatory support at a level sufficient to produce normal arterial blood gas values. Effective monitoring should be instituted to allow a rapid increase in ventilation and oxygenation should signs of increased ICP or hypoxemia occur.

Recommendations:

1. In the presence of increased ICP, maintain P_{aCO_2} 25 to 30 mm Hg or titrate to ICP if monitoring of ICP is available. Monitoring of ICP is desirable.

2. Maintain normocarbia in head-injured patients with normal ICP.

3. When hyperventilation is used to decrease ICP, return to normocarbia should be gradual (over 24 to 48 h).

Myocardial Ischemia and Congestive Heart Failure: In patients with myocardial ischemia, modes of mechanical ventilation that increase work of breathing will increase oxygen demand and may detrimentally affect the myocardial oxygen supply/demand relationship.[14,15] Resultant myocardial ischemia may decrease compliance of the left ventricle (LV). The increasing pulmonary capillary pressure and decreasing lung compliance create a vicious cycle, as resistance and work of breathing increase further. Therefore, in patients with myocardial ischemia and some combination of high lung resistance and/or poor respiratory muscle function, spontaneous ventilation associated with an increase in the work of breathing is likely detrimental.

In severe congestive heart failure, positive pressure ventilation (PPV) would be expected to decrease venous return. Positive pressure ventilation is likely to increase P_{aO_2} by increasing lung volume and reducing right-to-left shunting ($\dot{Q}_s/\dot{Q}_t$). Although the effect of PPV on the normal ventricle would be to decrease cardiac output by decreasing LV filling (preload), the effect of PPV on a dilated failing LV operating on the flat (depressed) portion of the cardiac function curve will be different.[16,17] In this circumstance, a reduction in transmural aortic pressure and associated decrease in wall stress and afterload might increase stroke volume.

Guidelines:

1. In the presence of acute myocardial ischemia, choose modes of mechanical ventilation that minimize work of breathing.

2. When life-threatening hypoxemia accompanies severe congestive heart failure, consider the potentially beneficial effect of PPV on decreasing venous return and improving oxygenation.

3. Consideration should be given for assessment of the effect of PPV on hemodynamics.

Neuromuscular Disease: Patients with ventilatory failure due to neuromuscular disease (*eg,* Guillain-Barré syndrome; cervical spinal cord injury) typically have normal ventilatory drive and normal or nearly normal lung function.[18] Because the primary physiologic defect is ventilatory muscle weakness, these patients are predisposed to develop atelectasis (from inadequate lung inflation) and pneumonia (from impaired cough and mucociliary clearance).[19,20] Their main needs during ventilatory management are provision of adequate lung inflation and aggressive airway management.[21] There is no evidence that either PPV or negative pressure ventilation is superior in this situation.

These individuals are at less risk for barotrauma than patients with intrinsic restrictive or obstructive lung disease, and they frequently prefer large tidal volumes (*eg,* 12 to 15 ml/kg). Typically, they are also more comfortable with high inspiratory flow rates. Whether full or partial ventilatory support should be provided depends on the patient's capabilities and the disease process: a patient with a high quadriplegia (*eg,* C1-2) lesion needs full ventilatory support whichever mode is used, whereas partial ventilatory support may be appropriate for individuals with some ventilatory capability, particularly during recovery, as long as patient comfort is maintained.

Guidelines:

1. Large tidal volumes (12 to 15 ml/kg) with or without PEEP (5 to 10 cm H_2O) may be needed to relieve dyspnea. Adjust peak flow rate as needed to satisfy patient inspiration needs (≥60 L/min peak inspiratory flow will typically be required).

2. Use total or partial ventilatory support based on the patient's inherent ventilatory muscle strength.

Obstructive Airways Disease (OAD): Acute respiratory failure in patients with asthma and chronic OAD is associated with significant expiratory obstruction and hyperinflation. Resistance to inspiration is likely to be greater in the patient with asthma because of airway edema and mucus. Both patient groups benefit from mechanical ventilation settings that maximize expiratory time, thus de-

creasing end-expiratory lung volume (V_{EE}), intrinsic (auto) PEEP, and the risk for hemodynamic compromise.[22] With the same tidal volume, a higher V_{EE} would produce a higher end-inspiratory lung volume (V_{EI}) and a greater risk for barotrauma.[23]

The use of high inspiratory flow rates will maximize expiratory time and minimize V_{EE} and intrinsic PEEP (auto-PEEP, dynamic hyperinflation). This is accomplished, however, at the expense of higher peak airway pressure (PAP) in the central airways. Although PAP generated by increasing flow rate does not correlate closely with barotrauma as well as plateau pressure, the amount of central airway pressure that is actually transmitted to the alveolus (the actual risk factor for barotrauma) is difficult to judge. End-inspiratory plateau pressure with volume-cycled breaths rises as dynamic hyperinflation increases and may be reflective of increasing risk of barotrauma.

Guidelines:

1. No evidence exists that one ventilator mode is better than another for initial management of OAD. The clinician should choose a ventilator mode he or she is familiar with and has used successfully in this setting.

2. Adjust the peak inspiratory flow rate to meet patient demands.[24]

3. Monitor for and minimize dynamic hyperinflation (auto-PEEP). See Section 4, A-6.

a. It is desirable to utilize the least $\dot{V}_E$ that produces acceptable gas exchange and leads to the greatest expiratory time. Maneuvers likely to accomplish this goal are as follows:

i. Decrease in $\dot{V}_E$
ii. Increase in expiratory time
iii. Acceptance of hypercapnia

b. When dynamic hyperinflation exists in the presence of patient-initiated mechanical ventilation, application of small amounts of ventilator-applied PEEP may be helpful in reducing the work of breathing (see Section 4, A-6). Application of ventilator PEEP above the level of initial auto-PEEP may lead to further hyperinflation and complications.

4. Based primarily on animal data and as discussed in the ARDS section, end-inspiratory plateau pressure is also a concern in OAD, as it reflects hyperinflation. We believe that attempts to maintain plateau pressure less than 35 cm H_2O are worthwhile even though the impact on patient outcome is unknown. In the acutely ill patient with OAD, measurement of plateau pressure usually requires sedation and paralysis.

5. Use of volume-cycled assist control ventilation in the initial treatment of the awake patient with OAD may be associated with significant risk of increasing hyperinflation and should be avoided.[25]

Asthma: 1. We believe that a high plateau pressure is predictive of hyperinflation of lung units in the patient with asthma. A high PAP may also predict hyperinflation. We recommend that plateau and peak pressures be minimized in patients with asthma. Unfortunately, PAP is significantly influenced by endotracheal (ET) tube size and inspiratory flows.

2. Accept an elevated P_{aCO_2}, as long as pH can be maintained at an acceptable level.[26,27]

3. Paralysis and/or sedation may be necessary in some patients if the ventilation mode cannot be matched to the patient's needs (*ie,* patient "fighting" the ventilator). Following paralysis and/or sedation, a decrease in active expiratory effort may be associated with less airway collapse. The associated decrease in CO_2 production (especially of respiratory muscles) may also be advantageous in some circumstances. Paralysis is associated with acute and long-term complications.

COPD: 1. Mechanical ventilation of COPD patients with acute respiratory failure is unlikely to require high PAP or to present problems with CO_2 removal. In the presence of high PAP or difficulty in CO_2 removal in patients with COPD, coexisting abnormalities should be considered (pneumothorax, pulmonary edema, mucus plugging, high degree of bronchospasm).

2. Patients with chronic respiratory acidosis should have alveolar ventilation titrated to pH, not P_{aCO_2}.

Postoperative Patients: Few patients require mechanical ventilatory support past the immediate postanesthetic period. However, residual anesthetic effects, usually due to narcotics or muscle relaxants, may require a variable period of mechanical ventilation. An anesthetic-induced decrease in FRC potentially coupled with thoracic or upper abdominal incision predisposes to atelectasis.[28,29] These patients with little or no significant lung disease may be optimally treated with relatively little difficulty. The greatest concern for the clinician is to avoid iatrogenic complications of ventilatory support, including infection, decreased cardiac output, prolonged support requiring unnecessary sedation, hyperventilation, inspissated secretions, and unnecessary exposure to potentially toxic high concentrations of inspired oxygen.[30,31] Often, patients are unnecessarily ventilated in the postoperative period because of the mistaken belief that mechanical ventilation *per se* is beneficial in establishing a more physiologic cardiopulmonary status. Thus, patients who have undergone major operative procedures involving the head, thorax, or abdomen may remain intubated and ventilated unnecessarily. Although prospective analysis has not determined whether such therapy has a significant rate of complication, to our knowledge, no prospective analysis has provided evidence of beneficial effects of such therapy. Future studies should be designed to determine which, if any, patients and/or surgical procedures require ventilatory support past the immediate anesthetic emergence period.

Unilateral Lung Disease: Patients with unilateral lung disease who require mechanical ventilation are infrequently encountered. Therapeutic efforts have included placement of double-lumen tracheal tubes to effect ventilation of each lung separately, positional changes of the patient, bronchial blockers, pneumonectomy, and alteration of inspiratory gas flows in order to improve overall lung function. Usually, such maneuvers ignore the effect of hypoxic pulmonary vasoconstriction on the affected lung and the

physiologic principles underlying inflation of the lung during PPV. Were it not for the restricting effect of the rib cage and diaphragm on lung inflation, the unaffected lung would receive the preponderance of the positive pressure breath and/or increase in lung volume secondary to application of CPAP. However, in the presence of an intact thorax, lung inflation depends on increase in transpulmonary pressure, the difference between airway and intrapleural pressure. The individual with unilateral lung disease usually has a marked discrepancy in compliance between the two lungs. A lung with marked decrease in compliance will receive less volume for a given applied airway pressure. Therefore, the noncompliant lung will be ventilated less than will the normal, compliant lung. Should such patients experience significant arterial hypoxemia and/or hypercarbia, more aggressive means of ventilatory support must be considered, as with any type of advanced lung disease. These might include $ECCO_2R$, ECMO, high-frequency ventilation, etc. The ability of these interventions to alter outcome is not known. To date, split-lung ventilation[32,33] with a double-lumen tracheal tube[34] and differential application of positive airway pressure has likewise not been shown to improve morbidity and mortality.

Guidelines

1. Initially utilize conventional ventilation techniques independent of presence of unilateral lung disease.

2. In the presence of difficulties in oxygenation, a trial of ventilation with the least involved lung in the dependent position is appropriate.

3. If PEEP is applied, initially utilize a single-lumen ET tube.

4. In cases of inability to oxygenate with traditional PEEP application, ILV with a double-lumen ET tube may be tried (synchronization of ventilation is not necessary). This mode of ventilation, however, has not been proved to alter outcome.

B. Discontinuation of Mechanical Ventilation

The consensus committee agreed there were many correct ways to discontinue patients from mechanical ventilation. There are a number of basic principles that are important in discontinuing ventilatory support and these are covered in Part 2 (Section 7). Specific recommendations are given below:

1. Whichever technique is used for discontinuation of ventilatory support, the clinician should know the signs of increasing ventilatory insufficiency and patient distress, and discontinue or modify the process if they appear, persist, or worsen:

(a) Increasing tachypnea (*eg*, beyond a total rate of 30 to 35 breaths/min) associated with patient distress.

(b) Agitation, panic, diaphoresis, or tachycardia, unrelieved by reassurance and adjustment of the mechanical ventilation system.

(c) Acidemia: acute drop in pH to <7.25 to 7.30, associated with an increasing P_{aCO_2}.

2. Excessive imposed work of breathing from demand valves or circuits, as indicated by substantial decreases in airway pressure during patient efforts, should be avoided during attempts at discontinuation of ventilatory support whether using a T tube or the ventilator circuit.

3. If intermittent mandatory ventilation (IMV) is used, the rate and degree of withdrawal of ventilatory support should be guided by pH, P_{CO_2}, total respiratory rate, heart rate, and signs of patient distress.

4. If pressure support ventilation (PSV) is used:

(a) The rate of reduction of the PSV level should be guided by total respiratory rate rather than by tidal volume. As a rule, respiratory rate should not exceed 30 breaths/min.

(b) If a patient can maintain adequate gas exchange and comfort level on a low level of PSV (*eg*, 5 cm H_2O), it is not necessary to reduce this to zero before extubation.

5. In patients in whom ventilatory support cannot be withdrawn successfully over a short period, a systematic approach should be taken to identify and treat contributing factors, such as the following:

(a) *Imposed loads* in the apparatus that increase work of breathing (*eg*, demand valves, small-diameter ET tubes).

(b) *Respiratory factors* (*eg*, bronchospasm, excessive secretions, pharmacologic depression of ventilatory drive, persistence of underlying disease, etc).

(c) *Nonrespiratory factors* (*eg*, cardiovascular dysfunction, increased metabolic rate, acid-base problems, hypophosphatemia, malnutrition, anxiety, etc).

6. In "difficult-to-wean" patients in whom discontinuation of ventilatory support occurs gradually over several days, it may be desirable to increase the level of support at night to enable the patient to rest effectively, as demonstrated by the ability to sleep.

7. Successful extubation requires the ability to protect the upper airway and clear secretions adequately in addition to successful discontinuation of ventilatory support. These factors should be considered and addressed both prior and subsequent to extubation.

Underlying Principles

Section 4: Physiologic Principles Relevant to Mechanical Ventilation

A. Patient-Related Physiologic Principles

The response to mechanical ventilation is governed by several physiologic relationships. Two cardinal rules apply:

1. Although the qualitative response of a given physiologic variable to manipulation of ventilator settings may be predictable, the quantitative response is highly variable and patient specific. Thus, an increase in PEEP or level of ventilation usually improves P_{aO_2} at a given F_{IO_2}. However, the extent of improvement in any given patient may be large or small, and the short-term improvement may produce complications due to the higher pressures (barotrauma). Likewise, an increase in $\dot{V}_E$ may be expected to result in a lower P_{aCO_2}, but the amount of reduction may be large

or small and must be balanced against the potential complications relating to the increase in ventilatory pressures.

2. A ventilator manipulation designed to improve one relation or variable may have undesirable effects on other equally important relations or variables. For example, an increase in PEEP may improve P_{aO_2} but adversely affect cardiac output, thereby negating the improvement in P_{aO_2} at the tissue level. Likewise an increase in $\dot{V}_E$ to reduce P_{CO_2} may result in greater auto-PEEP or adverse effects on cardiac output. The extent of negative side effects of a given ventilator manipulation is, again, highly variable and patient specific. The physiologic relations that are most important to consider are as follows:

1. *Ventilation Perfusion ($\dot{V}/\dot{Q}$ Relations):* The P_{aO_2} obtained at a given F_{IO_2} is a function of the uniformity (homogeneity) of distribution of ventilation and perfusion to different lung units. Units with relatively low ventilation and high perfusion are associated with incomplete oxygenation and, hence, a low P_{O_2} for a given F_{IO_2}. Units with no ventilation at all but which continue to receive perfusion contribute to shunting, which is one extreme of $\dot{V}/\dot{Q}$ inequality.

The distribution of ventilation among different units depends on the following:

(a) Whether the unit is aerated or not at end expiration; units that are air free at end expiration (due to atelectasis or fluid filling) require very high inspiratory pressures if they are to receive any ventilation at all.

(b) For aerated units, the distribution of ventilation is determined principally by regional compliance and resistance. Lung disease is invariably nonuniform, and this is the basic reason for the existence of serious $\dot{V}/\dot{Q}$ mismatching and for difficulty in oxygenation. On theoretical grounds, when the regional differences in mechanics are principally in resistance, distribution of ventilation should become more uniform with long inspiratory times (T_{IS}) and with decelerating flow patterns. Conversely, where the nonhomogeneity involves regional compliances, shorter T_{IS} and square flow pattern should result in more uniformity. Whether equalizing regional ventilation is good or bad for P_{aCO_2} is not entirely predictable, since improving $\dot{V}_E$ of a poorly ventilated unit may or may not be beneficial, depending on the state of perfusion of that unit. It is also evident that by rendering the $\dot{V}_E$ distribution more uniform, some units (usually the healthy ones) will receive less ventilation as the poorly ventilated units receive more. If perfusion is preferentially distributed to the former, overall $\dot{V}/\dot{Q}$ may worsen as distribution of $\dot{V}_E$ is improved.

The regional distribution of perfusion is determined principally by regional resistances in blood vessels supplying and draining different units. Regional resistances are related to gravity (dependent units have lower resistance), vasomotor tone, and mechanical factors (*eg*, lung volume and anatomic narrowing). Regional alveolar pressure (more appropriately, regional transpulmonary pressure) plays a critical role. When transmitted regional alveolar pressure is higher than pulmonary artery pressure (PAP), perfusion is arrested (West zone 1).

For a given degree of $\dot{V}/\dot{Q}$ mismatching and F_{IO_2}, P_{aO_2} is critically affected by mixed venous O_2 saturation (S_{vO_2}); lower venous O_2 saturation is associated with lower P_{aO_2}; S_{vO_2} is, in turn, dependent on cardiac output, metabolic rate, and hemoglobin.

From the standpoint of oxygenation, the primary beneficial effect of increased distending pressure (PEEP or greater tidal volume, V_T) is the recruitment of nonfunctional or very poorly ventilated units. The benefit can be enhanced or mitigated through secondary and unpredictable effects on the following: (1) the distribution of ventilation to other units (by upward displacement of these units to more favorable or less favorable segments of pressure volume curve); (2) the distribution of perfusion (through effects on the relation between Palv and PAP and on lung volume [and hence vascular dimensions]); and (3) on mixed venous P_{O_2} (through effects on metabolic rate [less or more fighting, less or more work of breathing] or cardiac output).

2. *Relation Between Ventilation and P_{aCO_2}:* The relation between minute ventilation ($\dot{V}_E$) and P_{aCO_2} is:

$$P_{aCO_2} = 0.863\ \dot{V}_{CO_2}/[\dot{V}_E\ (1 - V_D/V_T)]$$

where $\dot{V}_{CO_2}$ is CO_2 production in milliliters per minute STPD, a reflection of the metabolic activity of tissues, and V_D/V_T is equal to the tidal volume-dead space ratio.

This equation emphasizes the fact that P_{aCO_2} is determined by the relationship between metabolic rate and ventilation, and not solely by the absolute level of $\dot{V}_E$. The bracketed term reflects the fact that not all breathed gas ($\dot{V}_E$) is useful for CO_2 exchange; only the fraction ($1 - V_D/V_T$) is effective.

In normal subjects, much of the dead space (V_D) is due to the volume of the conducting airways (anatomic V_D). Since this volume changes little with V_T, V_D/V_T tends to decrease as V_T increases and V_D/V_T rarely exceeds 0.3 (*ie*, 30 percent of V_T). In ventilated patients, particularly those with intrinsic lung disease, V_D/V_T can reach extremely high values (*eg*, 0.7 to 0.8) and V_D is principally related to ventilated but poorly perfused lung regions (alveolar V_D). In such cases V_D/V_T need not decrease with an increase in V_T since the higher alveolar pressure required to generate the larger V_T may increase alveolar V_D (increasing the amount of zone 1, see above). Thus, quantitatively, the change in P_{aCO_2} as V_T is increased may not be predictable. The response of P_{CO_2} to changes in $\dot{V}_E$ is further confounded by possible effects of changes in ventilator settings on metabolic rate (see above equation). Thus, a patient may become more relaxed (and hence lower $\dot{V}_{CO_2}$) or more agitated as ventilator settings are adjusted. Increases in V_D/V_T and $\dot{V}_{CO_2}$ should be considered whenever a change in $\dot{V}_E$ does not result in the expected change in P_{aCO_2} or whenever a large $\dot{V}_E$ is required to maintain a reasonable P_{aCO_2}.

The above equation also emphasizes the effectiveness of accepting a higher P_{aCO_2} (permissive hypercapnia) or of lowering metabolic rate (*eg*, by sedation, paralysis) in reducing the required level of ventilation. A lower ventila-

tion is usually associated with lower distending pressures. To the extent that high distending pressures contribute to barotrauma and negative hemodynamic consequences, permissive hypercapnia and reductions in metabolic rate may help reduce the complications of ventilatory support.

3. *Thoracic Pressures and Cardiovascular Function:* Blood returns to the thorax along a pressure gradient from peripheral vessels to the right atrium (RA). To the extent that intrathoracic pressure affects RA pressure, it may alter the gradient for venous return. Since cardiac output cannot be different from venous return, an increase in intrathoracic pressure will, all else being equal, tend to reduce cardiac output. This effect is enhanced in the presence of hypovolemia.

Right ventricular (RV) output can also be affected by changes in RV afterload. The latter is affected in a complex way by lung volume; an increase in lung volume tends to increase the resistance of alveolar vessels while decreasing the resistance of extra-alveolar vessels. The net effect on total resistance is unpredictable. Changes in RV afterload can aggravate or minimize the effect of changes in intrathoracic pressure on RA pressure.

Changes in intrathoracic pressure also affect LV function; a higher intrathoracic pressure acts to reduce LV afterload. Where poor LV function is limiting cardiac output, an increase in intrathoracic pressure may result in better LV emptying, with secondary consequences on RV afterload (decrease) and venous return (increase). Changes in lung volume may also reflexly affect peripheral vascular tone.

It is clear that effects of changes in ventilator settings on hemodynamics are complex. However, in general, cardiac output is adversely affected by increases in intrathoracic pressure; the actual response varies.

4. *Tissue Oxygenation:* One of the main objectives of ventilatory support is to ensure that tissues are provided with their O_2 requirements. The rate at which O_2 is delivered to the issues (O_2 delivery [$\dot{D}_{O_2}$]) is a function of cardiac output ($\dot{Q}_t$), hemoglobin (Hgb), and O_2 saturation (S_{aO_2}). Thus:

$$\dot{D}_{O_2} = 1.39\ Hgb \times S_{aO_2} \times Q_t + 0.003 \times P_{aO_2}$$

D_{O_2} represents the theoretical maximum for O_2 consumption by the tissues. In practice, tissues cannot extract all the delivered oxygen. As D_{O_2} is reduced, the tissues are capable of increasing the fraction extracted such that their O_2 needs are met. A point is reached, however, where the fraction of O_2 that can be extracted reaches a maximum level. As O_2 delivery decreases below this critical level, the O_2 needs of the tissues cannot be met. This state (O_2 extracted < amount warranted by metabolic activity) may ultimately result in tissue damage and can, theoretically, account for multisystem failure in critically ill patients.

This critical level of O_2 delivery is related to the metabolic activity of tissues (the higher the activity, the higher the critical $\dot{D}_{O_2}$) and to the maximum fraction that tissues can extract from delivered O_2. In disease, metabolic rate (*ie*, $\dot{V}_{O_2}$) is often high. There is also evidence that in some clinical states (notably sepsis), the maximum fraction that can be extracted is reduced. Both factors tend to raise critical $\dot{D}_{O_2}$.

Mechanical ventilation affects two of the main determinants of $\dot{D}_{O_2}$, namely S_{aO_2} and $\dot{Q}_t$. Often, ventilator measures that are aimed at increasing one variable cause an opposite change in the other (*eg*, PEEP may improve S_{aO_2} but concomitantly may reduce $\dot{Q}_t$). Where maintaining a reasonable P_{aO_2} (*eg*, >60 mm Hg) requires PEEP in excess of 10 cm H_2O, it is important to consider whether the net effect (after allowing for possible adverse effects on $\dot{Q}_t$) is beneficial (*ie*, increase in $\dot{D}_{O_2}$), whether the remaining benefit, if any, warrants the extra risk of high PEEP or F_{IO_2}, and whether the same improvements in $\dot{D}_{O_2}/\dot{V}_{O_2}$ relation may not be accomplished less dangerously through reduction in metabolic rate or by increasing hemoglobin.

5. *Respiratory Mechanics:* The pressure required to produce a given tidal volume (V_T) in a given time (T_I = inspiratory time) is a function of the elastic and resistive properties of the respiratory system. The elastic properties are defined by the static pressure-volume (P-V) relation. This relation is sigmoidal with the system being most compliant (lowest elastance) in the midvolume range and becoming substantially stiffer near the upper (total lung capacity [TLC]) and lower volume extremes. Normally, end-expiratory volume is at about 40 percent of vital capacity (VC), and tidal changes in volume occur in the middle, most compliant, range. In ventilated patients, the V_T may be located near the upper or lower extremes of the P-V curve where the system is naturally stiff. The former situation—V_T encroaching on TLC—occurs under two conditions: (1) when VC is extremely small as a result of severe intrinsic lung disease; here, the flat portion of the P-V curve might lie within the target V_T; and (2) in the presence of high PEEP (external or intrinsic) which increases FRC.

Tidal volume occurs in the stiff range near residual volume (RV) under two conditions: (1) with obesity and abdominal distention which force end-expiratory volume (the starting position for the next breath) to be in the low range of VC. In this case, the increased stiffness is partially related to chest wall stiffness and partially to alveolar collapse. A variable portion of the applied pressure is, therefore, dissipated across the chest wall and not the lung (*ie*, less likelihood of barotrauma for the same distending pressure); and (2) when airway or alveolar closure occurs at higher than normal volumes. In this situation, airway closure may occur within the V_T range, and this derecruitment causes the lung to appear stiffer.

When measured compliance (V_T/[plateau pressure minus end-expiratory pressure (total PEEP)]) is too low, it is important to ascertain whether this is in part due to the V_T cycling near one of the volume extremes and, if so, whether cycling is occurring near TLC or RV. This has important implications both in terms of identifying the underlying pathophysiology (is the increased stiffness due to structural changes [true stiffness or not?]) and in defining the ventilator strategy to be used to minimize barotrauma. This distinction can be made with simple manipulations of ventilator output while monitoring airway pressure. One

simple approach is to decrease V_T for one to two breaths and then assess compliance with the smaller V_T. An increase in compliance as V_T decreases suggests that lung volume is near the stiff upper part of the P-V curve. An unchanged compliance indicates that V_T is cycling in the linear midrange. Conversely, if compliance decreases as V_T is lowered, volume is likely cycling near the stiff lower range of the P-V curve. In this case, addition of PEEP should improve the operating compliance (by raising end-expiratory volume toward the more compliant range). This should be helpful, particularly during weaning.

The conventionally measured compliance reflects the elastic properties of both chest wall and lung. A low measured compliance may be due to stiff lungs and/or a stiff chest wall or to a small fraction of the lung being ventilated (*eg*, ARDS). Increased lung stiffness is the predominant mechanism with intrinsic lung disease, with auto-PEEP, and where there is airway or alveolar closure in the V_T range (see above). Increased chest wall stiffness may be the predominant cause of decreased compliance with primary chest wall disease (*eg*, kyphoscoliosis) or where obesity or abdominal distention causes V_T to cycle near RV where the chest wall is naturally stiff (see above). Determination of the contribution of lung and chest wall to decreased compliance is possible only by concurrently (with airway pressure [Paw]) estimating pleural pressure using an esophageal catheter. Thus, if Paw during an inspiratory hold is 40 cm H_2O higher than end-expiratory pressure (PEEP) while the corresponding value from pleural pressures (Ppl) (*ie*, Ppl during plateau minus Ppl at end expiration) is 30 cm H_2O, then the lung contributes a quarter of the stiffness while the chest wall contributes three quarters, and so on. Where increased lung stiffness is the major reason for decreased compliance, the lung receives the brunt of the distending pressure and, all else being the same, the risk of barotrauma will theoretically be greater.

The other component to the distending pressure is that related to resistance. In ventilated patients, total resistance is made up of two components, ET tube resistance and resistance of the patient's airways. In many cases, ET tube resistance is the major component of total resistance. The resistance of the ET tube is not constant, but increases with flow rate. With the exception of obstructive diseases, the patient's resistance normalized for lung volume (specific resistance) is normally very small. In obstructive diseases, resistance is high and is often volume dependent, being higher at low lung volume. It should be remembered that the measured resistance value is determined by the size of the aerated compartment; thus, in ARDS (a condition in which the aerated capacity may be only one third of normal), the measured resistance value may be high, while the specific resistance is normal or low.

Whereas total elastance and total resistance determine the total distending pressure required to attain a given V_T in a given T_I, regional differences in respiratory mechanics can importantly influence the distribution of inhaled volume within the lungs. This may result in some lung regions becoming relatively overdistended even though total V_T may be reasonable. The regional distribution of V_T is affected in a complex way by the underlying reason for nonhomogeneity (*ie*, regional differences in resistance or compliance), T_I, and flow pattern.

The total distending pressure applied at any instant (Ptot) is the sum of pressure applied to overcome elastic recoil (Pel, a function of volume above passive FRC and the P-V curve), and the pressure applied to overcome resistive elements (Pres, a function of flow rate and resistance):

$$Ptot = Pel + Pres$$

In paralyzed or apneic patients Ptot is entirely supplied by the ventilator and Paw = Ptot. When the elastic and resistive properties are known, Ptot can be estimated. Any difference between Paw and Ptot is a reflection of the pressure generated by the patient. This approach can thus be utilized to assess the extent of patient effort and, hence, adequacy of ventilatory support.

6. *Dynamic Hyperinflation and Auto-PEEP:* Dynamic hyperinflation (DH) is defined as failure of lung volume to return to passive FRC (volume at which elastic recoil equals external PEEP) prior to the onset of the next inspiration. Whenever this happens, alveolar pressure remains higher than external PEEP throughout expiration, and unless airways completely collapse, expiratory flow continues until the onset of the next inspiration.

Auto-PEEP is the difference between alveolar pressure and external airway pressure at end expiration. A difference (*ie*, auto-PEEP) will always exist whenever expiratory flow continues until the end of expiration (this is the gradient for flow). In the passive patient, such a gradient can only result from dynamic hyperinflation since alveolar pressure in this case reflects only passive elastic recoil; a gradient thus means lung volume did not return to passive FRC. In the patient with active expiratory muscles, alveolar pressure is also affected by the pressure generated by expiratory muscles. A gradient (auto-PEEP) can therefore exist even though volume is at, or even below, passive FRC. Auto-PEEP in the active patient does not necessarily signify the presence of DH and its magnitude is not an index of the magnitude of DH. This is important to recognize, since the physiologic consequences and management of auto-PEEP due to dynamic hyperinflation and to expiratory activity differ (see below). Expiratory muscle activity frequently exists in the presence of high respiratory drive and/or high expiratory resistance.

Dynamic hyperinflation develops in the setting of high expiratory resistance or expiratory flow limitation and is influenced by the compliance of the respiratory system, the volume from which exhalation begins, and the expiratory time. In ventilated patients, the delay in emptying may be patient related (obstructive diseases) or, very commonly, may be due to "plumbing" problems (narrow ET tube, kinking or water clogging of exhalation tube, poor exhalation valve, etc). Measurement of Paw during expiration helps to distinguish between problems intrinsic in the patient and ET tube, from problems within the external circuit (high Paw during exhalation points to the latter causes).

Auto-PEEP (DH, air trapping, intrinsic PEEP) has been described in many conditions (*eg*, COPD, asthma, ARDS) and can occur whenever $\dot{V}_E$ is relatively high. Dynamic hyperinflation most commonly occurs, however, in the setting of severe airflow obstruction. Here, the ventilation requirements may be modest, but expiratory resistance is often severalfold greater than its inspiratory counterpart.

The consequences of DH are related to the associated changes in lung volume and pleural pressure. (1) It causes V_T to cycle closer to TLC where compliance is low (see above). More distending pressure is required to attain the same V_T. (2) It interferes with triggering in the assisted mechanical ventilation or pressure support modes; the patient has to generate enough pressure to offset auto-PEEP plus trigger sensitivity before triggering occurs. (3) Because of 1 and 2, it increases the work of breathing during weaning attempts. (4) It affects hemodynamics in a manner similar to external PEEP. (5) It can cause overestimation of the pressure difference required for tidal ventilation and subsequent underestimation of the true compliance of the respiratory system.

Auto-PEEP in the absence of DH (*ie*, end-expiratory lung volume at or below passive FRC) does not cause V_T to cycle near TLC (in fact, it may have an opposite effect by reducing end-expiratory lung volume below passive FRC), has little effect on triggering, does not increase work of inspiratory muscles (in fact, it may spare inspiratory muscle work through sharing of total work between inspiratory and expiratory muscles), and does not result in underestimation of true compliance. In fact, where volume begins below passive FRC due to expiratory muscle activity, the opposite (overestimation of compliance) may occur. Administration of external PEEP under these circumstances serves no purpose and may make it more difficult for expiratory muscles to reduce lung volume.

In the passive state, and for a given degree of expiratory obstruction, the two variables that are most critical in determining extent of DH are total $\dot{V}_E$ and the inspiratory/expiratory (I:E) ratio. A higher $\dot{V}_E$ will cause more DH whether the high $\dot{V}_E$ is the result of a large V_T or high rate (f). In the former case (larger V_T), more time is required to return lung volume to the passive FRC, whereas in the latter case (high f), less time is available to empty the same V_T. It is for this reason that reduction in $\dot{V}_E$ (through permissive hypercapnia or reduction in ventilatory demand) is one of the most effective ways of reducing DH. At a given f, the I:E ratio determines the time for delivery of the V_T. Higher values tend to increase auto-PEEP.

Measurement: Auto-PEEP should be suspected in all patients with airways obstruction or whenever the flow tracing demonstrates persistent flow at end exhalation. During *passive* ventilation (patient is not making respiratory efforts), auto-PEEP can be measured by comparing the end-expiratory airway occlusion pressure (easily measured in only a few currently available ventilators) with the set level of PEEP or by observing the amount of positive airway pressure required to initiate inspiratory flow. A helpful method for executing end-expiratory port occlusion in the passive patient uses the ventilator's inflation onset as the timing mechanism with a Braschi valve. Auto-PEEP can also be measured using plateau pressures. Operationally, plateau pressure is first recorded during a single cycle of volume-controlled ventilation at the usual ventilating frequency. (To avoid further hyperinflation, the end-inspiratory pause should not be applied for more than a single cycle.) Inflation is then prevented for approximately 20 s by a marked reduction in frequency, after which a single end-inspiratory plateau pressure is remeasured. The difference in plateau pressures is auto-PEEP.

Another similar method is first to measure the additional (dynamically trapped) volume released when a single routine tidal inflation is delayed by 20 to 30 s, and then to divide the measured trapped volume by respiratory system compliance. Under passive conditions, compliance is perhaps best judged by dividing the difference in static end-inspiratory ("plateau") pressures observed at two distinctly different V_T into that volume difference. This, however, is valid only if compliance is constant throughout V_T (*ie*, V_T is fully within the linear segment of the P-V curve).

In a passively ventilated patient, the effect of PEEP on lung and chest volumes can be accurately assessed by observing the peak dynamic or static airway pressures. Failure of these pressures to rise in response to adding PEEP indicates dynamic airway compression, flow limitation, and potential benefit to the addition of PEEP.

Finally, when auto-PEEP results from dynamic airway compression, the least PEEP increment required to evoke a detectable increase in lung volume or peak cycling pressure is sometimes considered to be the pressure required to counterbalance the original level of auto-PEEP. This technique is invalid, however, when expiration is not flow limited (*ie*, when DH is due to a simple increase in resistance and not to flow limitation). Moreover, the applied pressure needed to counterbalance the "critical" pressure approximates only 75 percent to 85 percent of the auto-PEEP determined by expiratory port occlusion.

In patients with active respiratory efforts (*ie*, assist mode, PSV, etc) auto-PEEP cannot easily be approximated by the end-expiratory occlusion, since expiratory muscle activity can influence the measured value. It can also be estimated as the esophageal pressure deflection required to initiate inspiration or to terminate expiratory flow. Interestingly, auto-PEEP estimated by this method is usually less than that measured by end-expiratory port occlusion. Although the reason for this disparity remains unclear, it has been argued that gas begins to flow into the lung when auto-PEEP in the least affected units has been overcome.

As indicated above, the auto-PEEP measured in patients with active respiratory efforts need not reflect dynamic hyperinflation. To our knowledge, there are currently no accepted methods of assessing the extent of DH in patients with active respiratory efforts. The use of external PEEP in these cases should be based more on clinical response to graded external PEEP (*ie*, more or less distress) than on the measured value of auto-PEEP.

7. *Respiratory Muscle Output and Endurance:* Laboratory studies have shown that inspiratory muscles fatigue when forced to generate pressures in excess of critical levels.[35] The critical pressure output above which fatigue occurs is a function of inspiratory muscle strength (*eg,* maximum inspiratory pressure). It is not clear whether fatigue occurs outside the laboratory setting, where inspiratory muscle output is spontaneously selected by the patient and not imposed (as in the laboratory). Nevertheless, the laboratory results point out the limited capacity of inspiratory muscles to sustain relatively high pressure outputs.

It is very difficult to assess the potential for fatigue in the ventilated patient. Whereas actual muscle output can be estimated through measurement of work of breathing, the pressure generated by muscle contraction or Pmus (see above), the denominator (maximum possible output) is difficult to determine. Furthermore, the critical fractions developed in the laboratory (*eg,* tension-time index >0.15) need not apply in the critically ill patient. So far, the best indication of whether the patient's muscles are overstressed remains the clinical impression of respiratory distress.

8. *Control of Breathing:* There is tremendous interindividual variability in the level of ventilation desired by patients (*ie,* ventilatory demand). The range extends from a few liters per minute (as in patients with chronic CO_2 retention) to > 30 L/min (*eg,* in sepsis). High levels of ventilatory demand are related to high metabolic rate (muscle activity, fever), excessive V_D/V_T, or to a lower CO_2 set point where the patient targets a subnormal P_{CO_2} (metabolic acidosis, neural reflexes, central problems). In the presence of high $\dot{V}_E$ demand, high $\dot{V}_E$ output by the ventilator is required in order for the patient to feel comfortable. In turn, high $\dot{V}_E$ output by the ventilator translates into greater distending pressure (more volume and flow) and greater tendency for auto-PEEP. In patients with high ventilatory demands, every effort should be made to identify the mechanism and, if possible, correct it. Should the distending pressures required to maintain comfort remain excessive, forced reduction in ventilatory drive through sedation and, if necessary, paralysis (to reduce metabolic rate) may be appropriate. At present, there are insufficient data to indicate the precise pressures (or volumes) that must be avoided (see complications, Section 5-B).

B. *Ventilator-Related Physiologic Principles*

During spontaneous unassisted breathing, contraction of the diaphragm and other accessory muscles of inspiration results in a decrease in intrathoracic pressure, followed by a corresponding decrease in alveolar and airway pressures. These decreased pressures cause an increase in thoracic volume and the movement of a V_T into the lungs. Relaxation of ventilatory muscles returns these pressures and volumes to their resting levels. That is, the elastic recoil of the thoracic cage and of the lung increases intrathoracic pressure, causing an increase in alveolar and airway pressure, allowing exhalation of the V_T. During mechanical ventilatory assistance, the magnitude and the direction of these pressures may be grossly altered with potential adverse effects as outlined elsewhere in this text. As a result, the appropriate selection of gas delivery settings and monitoring of system pressures is likely important.

1. *Ventilator Settings:*

(i) *Volume.* In volume-targeted (*ie,* volume cycled) ventilation, a machine-delivered V_T is set to be consistent with adequate gas exchange and patient comfort. The V_T selected in adults normally varies from about 5 to 15 ml/kg of body weight.[36,37] Numerous factors, such as lung/thorax compliance, system resistance, compressible volume loss, oxygenation, ventilation, and barotrauma, are considered when volumes are selected.[36] Of critical importance is the avoidance of localized overdistention.[38] This can generally be accomplished by selecting V_T that remain on the steep aspect of the P-V curve of the patient-ventilator system and by ensuring that peak airway and alveolar pressures do not exceed a maximum target.[37,39] Although controversy exists regarding specific target levels, many would agree that a peak alveolar pressure greater than 35 cm H_2O raises concern regarding the development of barotrauma and ventilator-induced lung injury increases.[37,40] With pressure-targeted (in pressure-limited) ventilation, delivered V_T varies depending on target pressure selected, system impedance, and the patient's spontaneous ventilatory pattern.

(ii) *Respiratory Rate.* Setting of mandatory ventilator gas delivery rate is dependent on the mode of ventilation selected, the delivered V_T, dead space to tidal volume ratio, metabolic rate, target P_{aCO_2} level, and level of spontaneous ventilation.[36] With adults, set mandatory rate normally varies between 4 and 20/min, with most clinically stable patients requiring mandatory rates in the 8 to 12/min range;[36] in patients with either acute or chronic restrictive lung disease, mandatory rates exceeding 20/min may be necessary, depending on desired $\dot{V}_E$ and the targeted P_{aCO_2}. Along with P_{aCO_2}, pH, and comfort, the primary variable controlling the selection of mandatory rate is the development of air trapping and auto-PEEP.[22] As with the selection of most ventilator settings, development of air trapping should be avoided because of its effect on $\dot{V}/\dot{Q}$ matching, work of breathing, and barotrauma.[22,41]

(iii) *Flow Rate.* The selection of peak inspiratory flow rate during volume-targeted ventilation is primarily determined by the level of spontaneous inspiratory effort. In patients triggering volume-targeted breaths, patient effort, work of breathing, and patient-ventilator synchrony depend on the selection of peak inspiratory flow.[42] Peak inspiratory flows should ideally match patient peak inspiratory demands. This normally requires peak flows to be set at 40 to 100 L/min, depending on $\dot{V}_E$ and drive to breathe. During controlled ventilation, peak flows may be set lower than 40 L/min in order to establish a specific T_I. With pressure-targeted ventilation, the peak inspiratory flow is determined by the interaction of the set pressure, respiratory resistance, and patient effort. The specifics of how *quickly* the pressure target is reached is defined by the manufacturer.

(iv) *Inspiratory Time/I:E Ratio.* The selection of a specific T_I and I:E ratio is generally based on hemodynamic response to ventilation, oxygenation status, and level of spontaneous breathing. In spontaneously breathing patients, gas delivery should be coordinated with patient inspiratory effort to ensure synchrony. This normally requires about 0.8 to 1.2 s and an I:E of about 1:2 to 1:1.5.[43] During controlled mechanical ventilation, T_I or I:E ratios may be lengthened in order to elevate mean airway pressure (MAP) and enhance oxygenation.[44] When lengthening T_I and I:E ratios, the impact of these alterations on the cardiovascular system must be carefully monitored. The primary factors limiting increases in both T_I and I:E ratios are patient discomfort, the need for sedation, the development of auto-PEEP, and hemodynamic compromise.[44]

(v) *Flow Profile.* Few data identifying differing physiologic responses to inspiratory flow profiles are available when adjusted for the same V_T and T_I/T_{TOT}.[45,46] Essentially no differences exist between square, decelerating, and sine wave delivery profiles in terms of gas exchange or work of breathing, and these approaches appear to be equally acceptable in the majority of patients requiring ventilatory support, provided that the mean flow rate is adequate. To our knowledge, no data supporting the use of an accelerating flow pattern are currently available. Selection of flow profile is available only in volume-targeted approaches to ventilation. With all pressure-targeted modes, an exponentially decelerating pattern is normally established as the ventilator attempts to rapidly achieve the pressure target set and to maintain the target constant throughout the inspiratory phase.

(vi) *Sensitivity.* Since mechanical ventilators and artificial airways impose a resistive load on the spontaneously breathing ventilator-assisted patient, ventilator-trigger sensitivity should be set at the most sensitive level that prevents self-cycling. Generally, this is –0.5 to –1.5 cm H_2O. Recently introduced flow cycling systems are generally more efficient than pressure cycling approaches, but the clinical significance of this is unclear.[2,47] These systems should also be set at maximum sensitivity (1 to 3 L/min).

(vii) F_{IO_2}. The selection of the F_{IO_2} is dependent on the target P_{aO_2}, PEEP level, MAP, and hemodynamic status. In general, as a result of concerns regarding the effect of high F_{IO_2} on lung injury, the lowest acceptable F_{IO_2} should be selected. However, the effect of F_{IO_2} on lung injury must be balanced by the effect of airway and alveolar pressures on lung injury. In those patients who are most difficult to oxygenate, F_{IO_2} can be minimized by optimizing PEEP and MAP, by deep sedation with or without pharmacologic paralysis, and by lowering the minimally acceptable S_{aO_2} to <90 percent while ensuring adequate cardiac output.[48]

(viii) *PEEP.* Positive end-expiratory pressure is applied to recruit lung volume, elevate MAP, and improve oxygenation.[49] PEEP may decrease venous return and preload of the LV,[50] as well as decreasing the triggering work of breathing caused by auto-PEEP.[41] The optimal level of PEEP depends on the desired physiologic response. In ARDS, PEEP level is established in conjunction with F_{IO_2} and T_I settings to establish a target P_{aO_2} (S_{aO_2}) or O_2 delivery. Although it is difficult to identify an upper limit for PEEP in this setting, most would agree that the lower limit should be at or above the lower inflection point on the P-V curve in the early phase of acute lung injury.[51] This is generally a PEEP level of about 8 to 12 cm H_2O. As with any pressure, avoidance of high PEEP levels is desirable.

2. *Pressure Measurements:* During the delivery of a positive pressure breath, system pressure can be measured in a number of locations (internal to the ventilator, at the airway opening, and at the carina). The farther away the measurement is from the alveoli, the greater the possible difference from actual alveolar pressure. During patient triggering, alveolar pressure is more negative than carinal pressure, which is more negative than airway opening pressures, which are more negative then internal ventilator pressures.[52] Because of resistance to gas flow during a positive pressure breath, pressure measured internal to the ventilator is greater than airway opening pressure, which is greater than carinal pressure, which is greater than alveolar pressure.[52] Pressure measured at all of these locations is only equal during periods of zero flow.

(i) *Peak.* Peak pressure is the maximum pressure obtainable during active gas delivery. In volume-targeted ventilation, peak pressure is dependent on both compliance and airways resistance, as well as V_T, peak flow, and flow pattern. For a given compliance and airway resistance, higher peak flow results in higher PAP. Generally, with all other variables equal, an accelerating flow profile results in a higher PAP than any other profile, since the highest flows are delivered with this pattern at end inspiration. With pressure-targeted ventilation, the peak inspiratory pressure is approximately equal to the target pressure. However, because of the high initial flow and the decelerating flow pattern in pressure-targeted ventilation, the initial system pressure may exceed the pressure target by about 1 to 3 cm H_2O.

(ii) *Plateau.* This is normally defined as the end-inspiratory pressure during a period of at least 0.5 s of zero gas flow.[43] It should be measured on the first breath after the setting of an inflation hold and requires passive ventilation. The plateau pressure is the pressure required to counterbalance end-inspiratory forces and roughly approximates the average peak alveolar pressure. With pressure-targeted ventilation, the pressure target approximates to the plateau (alveolar) pressure if a period (0.5 s) of zero delivered gas flow is observable.

(iii) *Mean.* The system pressure averaged over the entire ventilatory period is defined as the MAP. Because expiratory resistance usually exceeds inspiratory resistance,[53] MAP as displayed on monitoring devices almost always underestimates mean alveolar pressure (MalvP) to some extent.[44] The MalvP can be estimated from the MAP by the following formula:

$$MalvP = (\dot{V}_E/60)(R_E - R_I) + MAP$$

where R_I and R_E are inspiratory and expiratory resistances, respectively. Provided sufficient PEEP is applied to seek

out recruitable lung units, oxygenation and MAP demonstrate a predictable and quantifiable direct relationship.[44]

(iv) *End-Expiratory.* This is the airway pressure at the termination of the expiratory phase, normally equal to atmospheric or the applied PEEP level. However, in patients with prolonged expiration or short expiratory times, end-expiratory alveolar pressure may be further elevated as a result of the development of auto-PEEP. Alveolar and airway pressures are not the same unless periods of no-flow are established. That is, end-inspiratory airway pressure normally exceeds alveolar pressure because of resistance to gas flow, whereas end-expiratory alveolar pressure may exceed airway pressure because of the development of auto-PEEP and MalvP always exceeds MAP.

3. *Machine Problems:*

(i) *Demand Valves.* In all assisted modes of ventilation, the patient must activate gas delivery. This requires a pressure differential sufficient to trigger the ventilator. Once triggering occurs, sufficient gas flow must be provided to meet inspiratory demand. Both of these processes impose work on the patient. The amount of effort required to activate any given ventilator varies greatly and is generally greater with pressure triggering than flow triggering.[54] The addition of PEEP or CPAP may increase imposed work because of the adjustments the ventilator must make to maintain PEEP/CPAP during spontaneous breathing.[55] Although the work imposed by these systems is generally minimal, total imposed work of breathing can be significant when demand valves are considered in series with the work imposed by ET tubes and humidifier systems.

(ii) *Humidifiers.* Three different types of humidifiers are used during mechanical ventilation: bubble-through, passover, and artificial noses. Of these, the passover humidifier is the only one that does not have the potential to impose added work of breathing. Bubble-through humidifiers have minimal effect on imposed work of breathing if the machine sensing of patient effort is on the expiratory side of the circuit or at the circuit "Y." However, if patient effort is sensed on the inspiratory side, imposed work of breathing may be markedly increased because of the need to create a pressure gradient across the humidifier.[55] Artificial noses represent a resistance load placed in series with the ET tube and demand valve.[24] Their effect on work of breathing is dependent on length of use, patient ventilatory drive, and design of the valve.[56] In general, artificial noses should not be used in patients with marked ventilatory muscle dysfunction, particularly if small-sized ET tubes are used and if the development of auto-PEEP is an ongoing issue. Regardless of humidifier used, it should be able to establish at the carina a temperature of 30° to 32°C with an absolute humidity of 30 mg.[57]

(iii) *Apnea Ventilation.* Many ventilators do not incorporate backup apnea ventilation during pressure support or CPAP breathing. As a result, careful setting of low respiratory rate, low V_T, and low minute volume alarms are critical for the safe application of these modes of ventilation. In ventilators where apnea ventilation is available, apnea of definable time periods results in the provision of a backup control mode volume-targeted approach to ventilation. Resumption of spontaneous breathing or practitioner intervention re-establishes the original ventilatory mode.

C. *Patient-Ventilator Interactions*

The use of a mechanical ventilator often superimposes a clinician-selected pattern of ventilation on the patient's natural breathing rhythm. Under these circumstances, certain interactions between patient and ventilator will occur. These fall in two categories: (1) the response of the mechanical breath delivery system to patient efforts, and (2) the response of patient efforts to ventilator settings.

1. *Response of the Breath Delivery System to Patient Efforts:* If the ventilatory demands of the patient do not coincide with the quantity (or quality) of ventilation provided by the ventilator, patient-ventilator dyssynchrony can impose an inspiratory muscle load. This, in turn, leads to increased oxygen consumption of the respiratory muscles and patient discomfort, which is diagnosed as the patient "fighting" the ventilator. This detrimental patient-ventilator interaction may be due to the patient's "inappropriately" high ventilatory drive or to inappropriate ventilator settings or circuits. If the clinician determines that this problem is due to "inappropriate" patient demands, it may be appropriate to use sedation or paralysis to eliminate patient respiratory effort. Conversely, the problem may relate to the ventilatory mode or ventilator setup being used. These detrimental interactions between patient and ventilator can occur during any of the following phases of breath delivery.

(i) *Triggering.* Triggering is the initiation of gas delivery. Significant imposed ventilatory muscle loads can be imposed by insensitive or unresponsive triggering[54,58] systems. In addition, the presence of auto-PEEP,[41,59] narrow ET tubes,[60] obstructed airways, and stiff parenchyma[61] will serve to magnify the insensitivity or unresponsiveness of the triggering system. Attempts to maximize trigger sensitivity and responsiveness through demand valve adjustments or through the counterbalancing of auto-PEEP with applied PEEP are appropriate. Unfortunately, oversensitive valves can result in spontaneous ventilator cycling independent of patient effort.

(ii) *Gas Delivery.* Gas flow from the ventilator is governed (or limited) by a set flow (flow limited) or set pressure (pressure limited) on most ventilators.[62] Any patient effort during flow-limited breaths will only result in a decrease in airway pressure since additional flow above what is set is not available.[63,64] This can produce a significant imposed load on the ventilatory muscles. In contrast, any patient effort during a pressure-limited breath will result in an increase in flow but no change in airway pressure.[65,66] A patient's flow demands are thus theoretically more readily met by a pressure-limited breath strategy.[61,65] The capability of adjusting the rate of rise of airway pressure during pressure-limited breaths further enhances control of this variable.[67,68]

(iii) *Cycling.* On current systems, gas delivery can be terminated by set volume, set time, or set flow.[62] With volume

or time cycling, continued patient effort is ignored by the machine and this can lead to the patient's pulling against a closed inspiratory flow valve. Conversely, active expiratory efforts by the patient with volume or time cycling result in elevation in airway pressure that can result in automatic breath termination in association with a high pressure alarm limit. Flow cycling gives the patient more control than breath cycling.[62,65,66] Usually flow cycling is set to occur at 25 percent of peak flow. Increasing patient effort can thus delay cycling such that more gas is delivered. Conversely, decreasing efforts (or even initiation of expiratory efforts) cause these flow criteria to be met earlier and thus a smaller volume of gas is delivered over a shorter period. Synchrony between end of patient effort and end of pressure limiting is, however, not assured even with flow cycling.[66] Depending on the strength of patient efforts vs set pressure on respiratory mechanics, and on the flow level at which cycling occurs, pressure may continue beyond the patient's inspiratory effort (thereby interfering with expiration) or may terminate prematurely before end of patient effort.

2. *Response of Patient Efforts to Ventilator Settings:* Ventilator settings, such as V_T, flow rate, and pattern with flow-limited volume-cycled breaths, or the pressure level and rate of pressure rise with pressure-limited breaths are capable of the following: (1) altering the activity of mechanoreceptors in the airways, lungs, and chest wall; (2) altering blood gas tensions; and (3) eliciting respiratory sensations in conscious or semiconscious patients.[65,69] In turn, these can alter the rate, depth, and timing (T_I,T_E) of respiratory efforts through neural reflexes, chemical control (chemoreceptors), and behavioral responses. These changes in patient effort may modify expected responses to changes in ventilator settings. These modications may take several forms, including the following: (1) failure of $\dot{V}_E$ or V_T to change in the expected direction or to the expected magnitude as ventilator settings are changed to increase or decrease these variables; (2) periodic breathing, with periods of apnea, as P_{CO_2} cycles around the CO_2 set point; (3) loss of synchrony between patient and ventilator; and (4) changes in ventilatory demand (increase or decrease) as a result of altered level of consciousness (following a change in ventilator settings) or of changes in mechanoreceptor output (acting via reflex or behavioral mechanisms). There are very few systematic studies on the effect of various changes in ventilator settings on pattern of patient effort. This information is needed particularly with the current shift in emphasis from controlled ventilation methods to patient-interactive methods (*eg*, PSV).

Section 5: Complications of Mechanical Ventilation

Although mechanical ventilation offers vital life support, its use can result in untoward or life-threatening side effects.[70] Many such hazards can be modified or avoided by appropriate attention to the technique of implementation. Interventions associated with mechanical ventilation include airway intubation, application of positive pressure to the respiratory system, provision of supplemental oxygen, imposition of unnatural breathing patterns, and the administration of sedative or paralytic agents.

A. *Complications of Airway Intubation*

Endotracheal intubation is usually performed transnasally or transorally. The nasal route provides a more stable artificial airway and allows mouth closure, improving comfort in some patients. However, a bleeding diathesis is a contraindication to nasal intubation. Moreover, because a nasal tube is generally smaller than its oral counterpart, it presents greater flow resistance and may impede extraction of retained secretions from the central airways.[71] Sinusitis is a potential complication of ostial occlusion and impeded drainage by the nasal tube.

The artificial airway allows potential pathogens to enter the trachea from the external environment, dramatically increasing the risk of nosocomial pneumonia.[70,71] Moreover, disruption of the coughing mechanism and mucociliary escalator encourages retention of airway secretions. Endotracheal tubes prevent aspiration of gross particulates, but permit pharyngeal secretions to enter the trachea via the interstices of the balloon cuff, frequently resulting in tracheal colonization and increasing the risk of nosocomial pneumonia.

Tube misplacement and dislocation occur frequently. Although intubation of the right or (less frequently) left main bronchus most commonly occurs at the time of intubation, head movement may cause the tube orifice to migrate 2 cm in either direction from its neutral position along the tube axis. Overdistention of the ventilated lung and hypoventilation or atelectasis of the nonintubated lung are especially likely to occur in the heavily sedated patient receiving PPV. Hypoxemia, barotrauma, and cardiovascular compromise may result. Inadvertent extubation is among the most dangerous complications associated with mechanically ventilating a physiologically unstable patient; consequently, disoriented and uncooperative patients should be made as comfortable as possible, but they should be securely restrained.

Glottic injury often occurs during unusually difficult or emergency intubation. Glottic edema and minor erosive lesions of the vocal cords occur commonly during prolonged intubation. Postextubation glottic dysfunction and lasting damage to the vocal cords may occur, especially among women and among those patients in whom large tubes are placed. Risk factors for tracheal erosion, glottic stenosis, tracheal dilatation, and tracheomalacia are not precisely defined; however, cuff pressures that exceed capillary perfusion pressure ($\cong$ 25 cm H_2O) are likely to cause ischemic ulceration and more advanced forms of mucosal damage.[71] In the absence of reliable guidelines to indicate optimal timing, most practitioners reserve tracheostomy for those patients who are not making clear and steady progress after 2 to 3 weeks of therapy or for those with suspected abnormality of the upper airway. Tracheostomy af-

fords reduced V_D, partially restores glottic function, improves secretion clearance, enhances comfort, and holds the potential to allow both oral feeding and verbal communication. It may be associated, however, with life-threatening complications such as tracheal erosion, tracheoinnominate artery fistula (hemorrhage), and extraluminal migration of the tube orifice in the early postoperative period. Stomal granulation or stenosis are frequent problems after decannulation.

B. *Complications of PPV*

During PPV, the lungs and chest wall distend, intrathoracic pressure rises, and the lungs are often exposed to high inspired fractions of oxygen. In the setting of ARDS, for example, P_{aO_2} is improved by providing high fractional concentrations of inspired O_2 and by raising mean and end-expiratory alveolar pressures. Each of these interventions has an associated risk-benefit ratio. Although considerable experimental data have been accumulated, detailed clinical information is not yet available regarding which oxygen concentrations, pressures, and ventilation patterns are safe to apply for extended periods.

1. *Barotrauma:* For adult patients, flow-limited, volume-cycled ventilation using large V_Ts (10 to 15 ml/kg), rapid inspiratory flow rates, and PEEP when needed to adjust lung volume has previously been the standard of practice in managing most problems of ventilatory support.[72] Widely held objectives of ventilation have given priority to "normalizing" arterial blood gas values and ensuring adequate oxygen delivery. Until recently, respiratory system pressures have been monitored, but not tightly constrained.

There is little doubt that high ventilating pressures and excessive *regional* lung volumes are damaging. All forms of barotrauma that have been described previously in the pediatric literature, including interstitial and subcutaneous emphysema, pneumomediastinum, pneumoperitoneum, pneumopericardium, pneumothorax, tension cysts, systemic gas embolism, and damage similar to bronchopulmonary dysplasia, have now been recognized in adult patients, as well. Susceptibility to barotrauma may vary with the stage of the disease process; pressures well tolerated during the earliest stage of illness may prove excessive later on.[73] Many forms of barotrauma occur with increased frequency after ventilation for extended periods, especially in patients with ARDS.

It has been shown in a variety of animal models that ventilation with high V_Ts or high PAP can induce or extend acute lung injury.[74-80] In previously normal lungs, such damage is characterized by granulocyte infiltration, hyaline membranes, and increased vascular permeability. Fibroblast proliferation follows over a period of days.[79] Such lung injury occurs with peak inspiratory pressure (PIP) as low as 30 cm H_2O in normal sheep,[81] and with PIP as low as 20 cm H_2O in rabbits whose lungs have been lavaged with saline solution.[79] There are also suggestions from the experimental literature that ventilatory pattern influences the incidence and severity of injury, but further evidence is needed, and an optimal pattern has not been defined.[79]

Although ARDS has previously been considered a problem of *diffuse* lung injury and a generalized increase of tissue recoil, it now appears that the radiographic, densitometric, and mechanical consequences of ARDS are heterogeneous.[38,82] In severe cases, the inflation capacity of the lungs may be less than one third of normal.[38] The compliance and fragility of tissues comprising the aerated compartment in patients with ARDS may be closer to normal than previously envisioned, especially in the earliest phase of this disease. It is currently believed that ventilatory patterns that apply high transalveolar stretching forces cause or perpetuate tissue edema and damage.[74-76,79] Some experimental data suggest that large V_Ts, themselves, may also extend tissue edema, independent of the maximal pressure to which the alveolus is exposed.[75,80] It not clear, however, that large V_Ts are injurious when peak alveolar pressures are kept below 35 cm H_2O and sufficient PEEP is used to prevent widespread alveolar collapse and thereby maximize respiratory system compliance. Use of small V_Ts that avoid tissue overdistention and the acceptance of any consequent elevation of P_{aCO_2} (permissive hypercapnia) have been suggested to minimize the risk of barotrauma in patients with asthma and ARDS.[37,83,84] Although it remains unproved, some data suggest that periodic inflations with a relatively large volume may be needed to avert collapse of unstable lung units when very small V_Ts and low levels of PEEP are used.[77,79,85] In animal models, recruitment of lung volume by adequate amounts of PEEP can substantially reduce the ventilator-associated lung injury resulting from high PIP.[77,80] As yet, such application has not been shown to have a similar benefit in patients.

Strategies that prevent the exposure of the lung to high pressures (limiting overdistention) and those that lower the $\dot{V}_E$ requirement may be associated with less ventilator-induced tissue injury and improved outcome. Such approaches include permissive hypercapnia,[37,84] pressure-controlled ventilation,[86] and pressure-limited, volume-cycled ventilation.[87] Based on the experimental literature, maximal transalveolar pressure should not exceed 30 to 35 cm H_2O during each tidal cycle.[74,75,79] (This usually corresponds to 35 to 45 cm H_2O end-inspiratory static [plateau] pressure, depending on chest wall compliance.) In certain experimental settings, even pressures lower than this have been associated with tissue injury, especially when applied for extended periods. It may be desirable to allow spontaneous ventilatory efforts whenever it is possible to do so without incurring an excessive breathing workload or unbalancing the $\dot{V}_{O_2}/\dot{D}_{O_2}$ relationship. These modes, which include intermittent mandatory ventilation (IMV), pressure support, airway pressure release ventilation (APRV),[88] bi-level airway pressure, intermittent mandatory pressure release ventilation (IMPRV),[89] CPAP,[90] and various modes applied without airway intubation (noninvasive ventilation), tend to reduce maximal transalveolar pressure but do not guarantee a reduced incidence of barotrauma.

Adjunctive measures to conventional ventilation aimed at enhancing tissue oxygen delivery or increasing CO_2 removal (extracorporeal [$ECCO_2R$] or intracaval [IVOX] gas exchange[91] tracheal gas insufflation,[86] high-frequency ventilation [HFV]) decrease the exposure of the lung to high pressures (and volumes) and may, at times, allow better gas exchange than is otherwise possible. The success of these hazardous methods depends heavily on the skill with which they are applied. At the present time, their utility for general medical practice must be considered unproved.

2. *Oxygen Toxicity:* High fractions of inspired O_2 (F_{IO_2}) are potentially injurious when applied over extended periods.[92] In the laboratory setting, tissue injury depends on the F_{IO_2} and the duration of exposure. Because alveolar injury is an exponential function of inspired oxygen concentration (F_{IO_2}), even modest reductions in F_{IO_2} over the range of 0.6 to 1.0 may attenuate tissue damage. There is no convincing evidence that sustained exposure to $F_{IO_2} \leq 0.5$ causes tissue injury, and, for practical purposes, most clinicians do not attempt aggressive measures to reduce F_{IO_2} (*eg,* vigorous diuresis, inotropic pharmacotherapy, high levels of PEEP, experimental modes of ventilation, or adjunctive support) until the inspired O_2 concentration exceeds approximately 0.60. The combinations of O_2 concentration and duration of exposure that produce significant damage have not been firmly established in the setting of critical illness, and may well vary with disease type, severity, and individual susceptibility.

3. *Cardiovascular Complications:* Ventilatory support can help restore the balance between D_{O_2} and O_2 consumption when it alleviates an intolerable breathing workload. Conversely, PPV often impairs cardiac output by disturbing the loading conditions of the heart, as described earlier in Section 4, A-3.[93]

Mean lung volume or MalvP correlates best with the tendency of a given ventilatory pattern to cause hemodynamic compromise. *Under conditions of passive inflation,* MAP (as a clinically measurable reflection of MalvP) relates fundamentally to oxygen exchange, cardiovascular performance, and fluid retention.[44,94] The importance of each effect varies greatly in different patients. Mean airway pressure can be raised by adding PEEP, by extending the inspiratory time fraction (increasing I:E ratio), or by increasing $\dot{V}_E$. The tendency for an elevation of MAP to compromise hemodynamic performance is heightened by impaired cardiovascular reflexes and depletion of intravascular volume. The proportion of the alveolar pressure transmitted to the pleural space is determined by the relative compliances of the lung and chest wall:

$$\Delta \text{Ppl} = \Delta \text{Palv} \times (\text{Cl}/[\text{Cl}+\text{Cw}]).$$

Therefore, the hemodynamic effect of a given increment in MalvP will be accentuated when the lungs are relatively compliant and/or the chest wall is stiff. Hemodynamic consequences are predictably less when the patient makes spontaneous breathing efforts. For these reasons, dynamic hyperinflation occurring in a passively ventilated patient with severe airflow obstruction produces auto-PEEP that is particularly likely to cause hemodynamic compromise.[22,95] Auto-PEEP can be attenuated by reducing $\dot{V}_E$ or by reducing I:E ratio, thus increasing expiratory time.

Limiting tissue demand for oxygen and maintaining effective cardiovascular function are essential to an effective ventilation strategy. Recent studies suggest that survival in overt sepsis and sepsis syndrome correlates with oxygen delivery.[96,97] At the time of this writing, however, it is not clear whether therapeutic interventions that attempt to maximize O_2 delivery (when it is already in the normal range and there are no overt signs of hypoxia) or avoid depression of cardiac output improve outcome. Maximizing O_2 delivery may require expansion of intravascular volume, an intervention that has been associated with adverse outcomes in patients with acute lung injury.

4. *Breathing Effort and Patient-Ventilator Asynchrony:* The use of mechanical ventilation superimposes a clinician-selected pattern of ventilation on the patient's natural breathing rhythm. Circuits that impose substantial resistance and machines that respond poorly to the flow demands or cycling cadence of the patient may result in dyspnea and an unnecessary breathing workload. Factors that have been shown to increase the breathing workload during partial ventilatory support include ET tube resistance, excessive triggering threshold or response delay, insufficient flow capacity of the ventilator to meet peak patient demands, and the development of dynamic hyperinflation. The latter gives rise to auto-PEEP, which depresses the *effective* functional triggering sensitivity and may contribute to intermittent failure of the machine to respond to patient effort.[98] Inappropriately slow inspiratory flow rates may cause the patient to enter the expiratory phase of the tidal cycle before the volume-cycled breath from the machine has been completed, often resulting in conflict between the natural and the imposed breathing rhythms. The magnitude and importance of these effects is a direct function of $\dot{V}_E$.

Pressure-limited modes of ventilation (*eg,* pressure support) are theoretically unlimited with respect to meeting maximal flow demands; however, this ideal is seldom accomplished in practice. Such modes often present important problems of their own for the vigorously breathing patient. Pressure support, for example, although invaluable for overcoming ET tube resistance and for assisting the patient with moderate ventilatory requirements, is not well suited to the needs of a patient breathing at a rapid cycling frequency, one with variable ventilatory requirements, or one who has a very high airway resistance (especially from a very small ET tube). Tidal volume can fall dramatically as frequency increases, especially in patients with airflow obstruction. Moreover, a fixed level of pressure support cannot compensate for a change in ventilatory impedance or the development of auto-PEEP. A patient who requires a high level of pressure support when breathing at a rapid rate may find the applied level of pressure excessive when the ventilatory requirement abates.

C. *Adverse Effects of Sedation and Paralysis*

Sedation and paralysis are often required to allow patient comfort and to facilitate the imposition of ventilatory patterns (*eg*, inverse ratio ventilation [IRV]) which would otherwise conflict with the patient's own ventilatory pattern. Sedation may result in vasodilation that contributes to hypotension and reduced cardiac output. Paralytic agents immobilize the patient, encouraging secretion retention, atelectasis, and muscle wasting. With breathing efforts prevented, such patients are totally dependent on the ventilation set by the clinician and provided by the machine. Inadvertent disconnection of the ventilator circuit can prove rapidly catastrophic in this setting. Certain neuromuscular blocking agents have been recently associated with neuromuscular weakness that persists long after withdrawal of drug treatment.[99] At present, it is not certain whether such effects relate primarily to the nature, dose, or duration of the drug, to synergism with corticosteroids, or to the depth of paralysis itself.

D. *Other Complications*

Among the wide variety of noncardiopulmonary complications that have been described for mechanical ventilation, perhaps the most important involve mental distress and dysfunction of the renal, gastrointestinal, and central nervous systems. Psychological distress during mechanical ventilation is exceedingly common, for reasons that include (but are not limited to) sleep deprivation and impaired sleep quality, pain, fear, inability to communicate, and the use of drugs (*eg*, benzodiazepines) with dissociative properties.

Renal dysfunction during PPV is believed to be a consequence of reduced circulating blood volume. This tends to alter perfusion of the renal parenchyma, redistribute intrarenal blood flow, release antidiuretic hormone, or inhibit atrial natriuretic peptides. In any event, reduced free water clearance and generalized fluid retention are commonplace during ventilation with high pressures.

Gastrointestinal consequences of mechanical ventilation include gut distention (due to air swallowing), hypomotility, and obstipation (due to pharmacologic agents and immobility), vomiting (due to pharyngeal stimulation and motility disturbances), and mucosal ulceration and bleeding. Serious dysfunction of the liver that occurs as a direct consequence of mechanical ventilation is rare. However, PEEP has been associated with hyperbilirubinemia and mild elevations of liver enzyme levels in the serum, possibly related to altered hepatic perfusion and impeded venous and biliary drainage.

Increased intrathoracic pressure can elevate jugular venous and intracranial pressures, and thereby reduce cerebral perfusion pressure. Such effects assume particular importance in the setting of reduced mean arterial pressure and reduced intracranial compliance resulting from head injury or surgical intervention. The risk of intracranial hypertension in patients ventilated with high MAPs is attenuated by conditions that limit transmission of alveolar pressure to the pleural space (low ratio of lung to chest wall compliance).

Section 6: Specific Modes of Ventilation

A. *Standard Modes*

1. *Introduction:* Assisted modes of ventilation are those in which part of the breathing pattern is contributed or initiated by the patient. The work of breathing performed by the patient is never abolished, and one of the difficulties for the physician is to determine the appropriate settings to match the patient's demand, both in terms of gas exchange and work of breathing. The main reasons for using assisted modes in the ICU are the following: (1) to synchronize patient and ventilator activity; (2) to reduce the need for sedation; (3) to prevent disuse atrophy of the respiratory muscles; (4) to improve hemodynamic tolerance of ventilatory support; and (5) to facilitate the weaning process.

Significant differences exist among ventilators concerning demand-valve sensitivity and opening delay, the algorithm for pressure support (PS) (rise in pressure, mechanism, and criteria for cycling from inspiration to exhalation, plateau pressure), flow-impedance characteristics of the expiratory circuit, and equipment. A great deal of data obtained experimentally and in patients suggest that these differences may alter the work of breathing.[55,58,100] Many of the proposals listed below may be modified by the quality of the equipment used.

2. *Assist-Control (A/C):* This is a mode of ventilation in which every breath is supported by the ventilator. A backup control ventilatory rate is set; however, the patient may choose any rate above the set rate. Until recently, most ventilators using this mode delivered breaths that were volume cycled or volume targeted. Using volume-targeted, A/C ventilation, the V_T, inspiratory flow rate, flow waveform, sensitivity, and control rate are set. Most of the data in the literature concerning A/C were obtained with this mode.[25,42,63,101] Pressure-limited or pressure-targeted A/C in which pressure level, T_I, control rate, and sensitivity are set is now available on several ventilators.

Advantages: Assist-control ventilation combines the security of controlled ventilation with the possibility of synchronizing the breathing rhythm of patient and ventilator, and it ensures ventilatory support during every breath.

Risks or Disadvantages: (1) Excessive patient work occurs in cases of inadequate peak flow or sensitivity setting, especially if ventilatory drive of the patient is increased (volume-targeted A/C);[25,42,101] (2) it may be poorly tolerated in awake, nonsedated subjects and can require sedation to ensure synchrony of patient and machine cycle lengths; (3) it may be associated with respiratory alkalosis; (4) it may potentially worsen air trapping in patients with COPD; and (5) if pressure-targeted A/C is used, there is risk of variable (and potentially markedly decreased) V_T during changes in lung impedances, patient ventilatory drive, or patient-ventilator dyssynchrony.

Patient work of breathing or effort during volume-targeted A/C is dependent upon sensitivity, flow rates (flow rate lower than 40 L/min should probably be avoided), and respiratory drive of the patient. This is dependent on many stimuli, including fever, anemia, hypoxia, pain, hypovolemia, level of consciousness, etc. Since patient work is dependent on the ability of the ventilator to rapidly recognize patient effort and provide sufficient flow to meet inspiratory demand, the set-up of the ventilator may play an important role in the patient's tolerance of this mode.[63,101] With pressure-targeted A/C, the ventilator, once triggered, provides sufficient flow to allow the set pressure plateau level to be achieved rapidly. As a result, concern with excessive patient work is potentially minimized in pressure-targeted A/C.

3. *Synchronized Intermittent Mandatory Ventilation (SIMV):* Synchronized IMV is a mode of ventilation and a mode of weaning that combines a preset number of ventilator-delivered mandatory breaths of predetermined V_T with the facility for intermittent patient-generated spontaneous breaths.[102,103] Similar to A/C, several ventilators offer the possibility of delivering pressure-targeted breaths instead of volume-targeted breaths during mandatory cycles. Mandatory breaths can be patient triggered with SIMV; however, if patient effort is not sensed within a specific period, the ventilator delivers a mandatory breath. Pressure support (see below) may be applied during nonmandatory breaths.

Set-Up Parameters. These include V_T, flow rate and/or T_I, frequency of controlled breaths, and sensitivity. When pressure-targeted breaths are used, pressure level and T_I must be set.

Advantages. (1) The patient is able to perform a variable amount of respiratory work and yet there is the security of a preset mandatory level of ventilation; (2) SIMV allows for a variation in level of partial ventilatory support from near-total ventilatory support to spontaneous breathing; and (3) can be used as a weaning tool.[102]

Risks. With IMV, there are risks of dyssynchrony between the patient effort and machine-delivered volume.

With SIMV the risks are as follows: (1) hyperventilation and respiratory alkalosis are possible, similar to A/C. (2) Excessive work of breathing due to the presence of a poorly responsive demand valve, suboptimal ventilator circuit (its impedance will vary with the particular ventilator used), or inappropriate flow delivery could occur. In each case, extra work is imposed on the patient during spontaneous breaths. This work can be minimized or abolished with the addition of pressure support. (3) Worsening dynamic hyperinflation has been described in patients with COPD.

The total work (or power) performed by the patient is dependent on the number of mandatory breaths. It was initially thought that the effort performed by the patient was virtually zero during mechanical breaths. However, recent data suggest that the muscular effort of the dyspneic patient during machine-assisted breaths does not vary substantially from the unassisted cycles on a breath-to-breath basis, *ie,* at the same overall level of ventilator support, effort is more or less independent of whether or not the breath is assisted.[64] The work of breathing may also vary with the addition of pressure support during spontaneous cycles and with the use of pressure-targeted mandatory breaths. There has been no demonstrated advantage of using IMV or T-piece trials in terms of reducing weaning duration.[104,105]

4. *Pressure Support Ventilation (PSV):* Pressure support ventilation is a pressure-targeted, flow-cycled, mode of ventilation in which each breath must be patient triggered. It is used both as a mode of ventilation during stable ventilatory support periods and as a method of weaning patients.[55,65,106-111] It is primarily designed to assist spontaneous breathing, and therefore the patient should have an intact respiratory drive.

With PSV, at the onset of inspiration, the pressure rises rapidly to a plateau that is maintained for the remainder of inspiration. The patient and ventilator work in synchrony to achieve the total work of each breath. On most ventilators, termination of inspiration occurs when a flow threshold is reached during the decelerating phase of inspiratory flow. That is, the breath is flow cycled to exhalation (this has been made possible by incorporating pneumotachographs in the ventilators). To avoid confusion, it should be stressed that the difference with pressure-targeted A/C, described above, is that termination of inspiration is different: it is time cycled for pressure-targeted A/C (*ie,* the T_I is fixed), whereas it is flow cycled for pressure support, *ie,* airway pressurization always stops before reaching the zero flow, and inspiratory duration is dependent on patient's effort.

Set-Up Parameters. These include pressure level and sensitivity. No mandatory PS rate is set; however, many ventilators incorporate volume-targeted back-up modes in the event of apnea. In some ventilators, it is possible to adjust the rate of rise in pressure at the beginning of inspiration or to adjust the flow threshold for cycling from inspiration to expiration.

Advantages. (1) As a result of the patient having significant control over gas delivery, overt dyssynchrony is less likely than with A/C or SIMV. When the PS level is chosen appropriately, this mode is generally regarded as comfortable for most (but not all) spontaneously breathing patients.[65,106] (2) Pressure support ventilation reduces the work of breathing roughly in proportion to the pressure delivered and is associated with a decrease in respiratory frequency and increase in V_T with increasing levels of PS.[65,106,108] These breathing pattern characteristics may be useful in selecting the appropriate PS level. (3) Pressure support ventilation can be used to compensate for the extra work produced by the ET tube and the demand valve.[107,108] (4) It allows for a wide variation in the level of partial ventilatory support from nearly total ventilatory support (high pressure levels) to essentially spontaneous breathing. (5) Pressure support ventilation may be useful

in patients who are "difficult to wean." Preliminary data suggest either no difference when compared with other modes or a shorter weaning duration and a higher success rate in selected patients using pressure support.

Disadvantages. Tidal volume is not controlled and is dependent on respiratory mechanics, cycling frequency, and synchrony between patient and ventilator. Therefore, careful monitoring is recommended in unstable patients; a back-up $\dot{V}_E$ seems necessary for safety; hypoventilation may develop during continuous-flow nebulizer therapy. Pressure support ventilation may be poorly tolerated in some patients with high airway resistances because of the preset high initial flow and terminal inspiratory flow algorithms. This may be improved, however, with adjustment of initial flow rates, which is possible on new systems.[67,68]

Work of Breathing. Increasing PS levels decrease respiratory effort as indicated by a number of changes in breathing pattern. This mode can be combined with SIMV[111,112] and has been used to compensate for the additional work of breathing due to the ET tube and the demand valve, adding PS (5 to 10 cm H_2O) during the nonmandatory breaths.[107,108] Higher levels of PS can also be used, combining mandatory and supported breaths. At the present time, clinical studies are lacking to demonstrate the superiority of one mode of partial ventilatory assistance over others. Pressure support has been widely accepted in many ICUs, and, for some physicians, it seems to be the most useful modality for delivering assisted ventilation either as full ventilatory support or as a mode for gradually withdrawing mechanical ventilation. For others, it is a useful adjunct to existing modes.

5. *Continuous Positive Airway Pressure (CPAP):* Continuous positive airway pressure is a mode designed to elevate end-expiratory pressure to levels above atmospheric pressure to increase lung volume and oxygenation.[113] A constant positive airway pressure is supplied by the ventilator throughout the ventilatory cycle; all breaths are spontaneous. It is also proposed as a means of reducing the pressure gradient between the mouth and the alveoli in patients with air trapping.[41,59] It is designed to assist spontaneously breathing patients and therefore requires an intact respiratory drive.

Until recently, two main types of CPAP systems were used. Those offered by most mechanical ventilators work via a demand valve that needs to be opened to deliver the gas to the patient. This demand valve is pressure triggered or flow triggered. Other specially designed systems work on the principle of a continuous high flow of pressurized gas in the external circuit from which the patient can breathe spontaneously. The advantage of the first system is that ventilator monitoring is still available, but the major drawback is that work of breathing is increased by the presence of a demand valve. A continuous-flow system is incorporated in some mechanical ventilators in an attempt to combine the advantages of the two previous systems.[47,114] In this mode, an adjustable, constant flow of gas is continuously delivered in the external circuit during the expiratory phase. Both the inspiratory flow and the expiratory flow are measured and compared by the machine. A difference between these two flow rates indicates to the ventilator that inspiration or expiration is occurring, leading to an adjustment in the delivered flow rate.

Set-Up Parameters. These include pressure level and sensitivity: level of negative pressure (demand valve system) or flow threshold and basal flow rate (continuous-flow systems and/or flow-triggered systems).

Advantages. CPAP offers the benefits of PEEP to spontaneously breathing patients. It will improve oxygenation if hypoxemia is in part secondary to decreased lung volume; it may recruit collapsed lung units, minimizing the work of breathing and improving oxygenation. It may help to reduce the work of breathing in patients with dynamic hyperinflation and auto-PEEP.

Recent data suggest that the work of breathing is reduced with systems incorporating a continuous-flow system in comparison to demand valve systems.[47,114]

Risks. Hyperinflation and excessive expiratory work may result if excessive CPAP levels are used. Poor clinical tolerance may increase inspiratory work of breathing, if hyperinflation is produced or if nonthreshold PEEP devices are used. There will be increased expiratory work if hyperinflation is produced or if PEEP devices with large flow resistances are used. The use of demand valves with intubated patients receiving CPAP may lead to patient-ventilator dyssynchrony.

This mode can be used in intubated patients as well as nonintubated patients (*eg,* patients with sleep apnea). Although inspiration is not really assisted, modern ventilators deliver a small level of pressurization, *ie,* a 1 to 3 cm H_2O level of pressure support, to avoid negative airway pressure relative to the end-expiratory level during inspiration. It is not clear, however, whether this has a significant clinical effect.[58]

6. *Servo-Controlled Modes:* Servo-controlled modes are used both for ventilation and for weaning patients. The basic principle is the use of a feedback system to control a specific variable within a given narrow range.[115-117] The ventilatory mode is either SIMV or PSV. The targeted parameter is set by the physician and can be either $\dot{V}_E$ or a component of the breathing pattern (respiratory rate, V_T).

Examples of servo-controlled modes include the following:

(i) *Mandatory Minute Ventilation (MMV).* MMV relies on a patient's spontaneous breathing to meet a predetermined $\dot{V}_E$. If this goal is not met, mechanical breaths at predetermined volume are delivered with a rate sufficient to supply the required $\dot{V}_E$. Here the targeted parameter is $\dot{V}_E$. In some ventilators used to implement MMV, the basic mode is SIMV; in others, it can be PSV.

(ii) *Servo-Controlled PSV (With the Exception of MMV).* The underlying mode is PSV and the targeted parameter is respiratory rate or V_T. If the targeted value is not met, the ventilator can either modify the pressure target level or the way the breath is cycled. The regulation of the targeted

variable varies among ventilators. It can take different forms: volume-assured PS, pressure augumentation, volume support, pressure-supported breaths, and volume-assisted breaths.

(iii) *Knowledge-Based Systems.* More complex systems have been implemented in microcomputer-driven ventilators and are being studied or are already used for the routine treatment of patients in specialized centers.[9,118-120] These systems have been proposed to help in the treatment of patients with ARDS or to automatically wean patients from mechanical ventilation. At the present time, none of these systems is commercially available.

Advantages include adaptation of the ventilator to the needs of the patient. These systems try to combine the advantages of a partial ventilatory support with the variability in the needs of the patient.

Disadvantages include the following: (1) The algorithm may induce nonphysiological breathing patterns. (2) The adequate target value can be difficult to adjust (*eg,* adequate level of $\dot{V}_E$ for MMV). (3) Measurement of $\dot{V}_E$ may give false information if breathing pattern is not considered (rapid shallow breathing may go unrecognized). The published data and clinical experience with these modes are minimal.

B. *Alternate Modes of Ventilation*

1. *Introduction:* During the last decade, a new concept has emerged regarding acute lung injury. In severe cases of ARDS, only a small part of the lung parenchyma remains accessible to gas delivered by the mechanical ventilator. This is widely known as the "*baby lung*" concept. As a consequence, V_T of 10 ml/kg or more may overexpand and injure the remaining normally aerated lung parenchyma (see Section 5, B-1) and could worsen the prognosis of severe acute respiratory failure by extending nonspecific alveolar damage.[121] Because lung volumes and airway pressures relationships are determined by the respiratory P-V curve, and because the apparent "stiffness" of ARDS lung appears related to the fraction of aerated lung, rather than to a generalized increase in elastic recoil, *the specific compliance of the remaining aerated lung parenchyma may be nearly normal.* High airway pressures may result in overdistention and local hyperventilation of more compliant parts of the ARDS lung.[39] Overdistention of lungs in animals has produced diffuse alveolar damage.[75,122] There are also data in the literature suggesting that ventilation using relatively low end-expiratory pressures (less than the inflection point [opening pressure] of the pressure-volume curve) causes progression of lung injury in animal models of ARDS.[123] This is the reason why alternative modes of mechanical ventilation—all based on a reduction of end-inspiratory airway pressures and/or V_T delivered to the patient and some based on ventilation between the lower and upper inflection points of the P-V curve—have been developed and are clinically used by many physicians caring for patients with severe forms of acute respiratory failure. Three of them, HFV, IRV, and airway pressure release ventilation (APRV), will be described in this section. Since, to our knowledge, there are no data demonstrating the superiority of these nonconventional ventilatory modes in terms of morbidity and mortality, only their physiologic rationale and their putative advantages and disadvantages will be presented.

2. *High-Frequency Ventilation (HFV):* High-frequency ventilation is the administration of small V_T—1 to 3 ml/kg—at high frequencies—100 to 3,000/min.[124] Because it is a mode of mechanical ventilation based on a marked reduction in V_T and airway pressures, it has the greatest potential for reducing pulmonary barotrauma. Mechanisms of gas transport change from conventional bulk flow $[V_A = (f)(V_T - V_D)]$ to other types when $V_T < V_D$. Proposed mechanisms include coaxial flow, Taylor dispersion, pendelluft, and augmented molecular diffusion. Under these conditions, the $(f)(V_T)$ product is usually much higher than during conventional mechanical ventilation and V_A appears to be more influenced by V_T than f. There are a number of different types of HFV. The three most common are high-frequency oscillation, high-frequency PPV, which is used in anesthesia, and high-frequency jet ventilation (HFJV), which is used both in anesthesia and in critically ill patients with acute respiratory failure. HFJV is the only high-frequency mode routinely used to ventilate patients with ARDS, mainly in Europe. Convincing comparative data concerning the advantages of HFJV over conventional mechanical ventilation (CMV) have been presented in the following limited number of clinical studies. There is no agreement, however, that HFJV is better than CMV in these situations: in ARDS patients with circulatory shock,[125] in cardiac patients with low cardiac output state,[126] and in patients with tracheomalacia, BPF, and tracheoesophageal fistula.[127]

In one well-controlled multicentered clinical trial (the HIFI trial), high-frequency oscillation was found not to be superior to CMV in ventilation of neonates with infant respiratory distress syndrome, but this study has been criticized because of the lack of a volume recruitment protocol.[84] In a number of animal studies, ventilation above the inflection point is required for the beneficial effects of HFV;[128,129] HFV may need to be implemented early in the course of the disease to be effective.

Because of the risk of gas trapping related to expiratory flow limitation, HFV is generally contraindicated for asthma and COPD. Although some European groups routinely use HFJV in combination with low V_T conventional ventilation to treat patients with severe forms of ARDS (8 to 10 tidal volumes per minute of 3 to 4 ml/kg superimposed on HFJV), there are no convincing data demonstrating the superiority of this method of mechanical ventilation in terms of pulmonary barotrauma and mortality. It must be pointed out that the only prospective randomized study comparing HFJV with conventional ventilation, which was performed in a nonhomogeneous population of cancer patients with ARDS, did not demonstrate any significant advantage for one or the other method.[130] HFJV can be safely administered in the clinical setting of the ICU according to the following guidelines:

(i) Clinicians must be very familiar with the technique (ventilatory settings, types of injection, humidification).

(ii) Like all other forms of HFV, HFJV, when administered for periods longer than 8 h, requires adequate humidification of delivered gases or severe necrotizing tracheobronchitis can occur.[131] Because the pressure drop across the injection system is very large *(the operating pressures are between 1 and 3 atmospheres, whereas MAP is between 1 and 30 cm H_2O)*, gas expansion occurs within the trachea causing cooling. Therefore, specially designed devices for providing adequate humidification during HFJV are required. One such device is a specially constructed high-temperature vaporizer.[127] Many detrimental effects of HFJV are, in fact, due to inadequate humidification.

(iii) The effects of ventilator parameters related to airway pressures and V_T are reasonably well understood. Respiratory effects of changing ventilatory settings are markedly influenced by the patient's respiratory mechanics. Increasing I:E ratio and driving pressure increase FRC and V_T. Increasing respiratory frequency markedly decreases V_T and increases P_{aCO_2} and has minimum effect on FRC in patients with stiff lungs.[132] The more compliant the respiratory system, the larger the increase in FRC induced by increasing I:E ratio, driving pressure, and respiratory frequency.

(iv) Mean airway pressure should be continuously monitored using an intratracheal catheter located at least 5 cm below the injection site. It has been demonstrated in experimental[133] and clinical conditions[134] that MAP measured during HFJV is a reasonably good reflection of MalvP in patients *without* significant obstruction.

(v) There is a large body of evidence in various animal models that HFV is most effective in diseases with stiff lungs when applied following a volume recruitment maneuver. The aim is to ventilate the lung at a pressure above the inflection point, yet at pressures sufficiently low not to cause high pressure (or volume) damage to the lung.[135] This approach has been used in neonates with success, but, to date, these clinical trials have been relatively small.

Potential Risks. Due to the large flow rates used and the fact that gas transport is less well understood, HFV is inherently more dangerous than CMV. Outflow obstruction can rapidly lead to increases in lung volume and attendant hemodynamic compromise and barotrauma. Air trapping due to the high flow rates is always of concern, especially in patients with compliant lungs and airways obstruction. Air trapping can be assessed by measuring airway opening pressure under static conditions after airway occlusion, by monitoring esophageal pressure, or by measurements of lung volume obtained at the chest wall (*eg*, inductive plethysmography). Inadequate humidification can induce severe necrotizing tracheobronchitis as described above.

3. *Inverse Ratio Ventilation (IRV)*: Inverse ratio ventilation is the use of I:E ratio > 1:1 during CMV.[87] There are two different types of IRV: pressure-controlled (pressure-limited) IRV, where the ventilator generates a servo-controlled square wave of pressure to the airways via a decelerating inspiratory flow, and volume-cycled IRV, where the ventilator generates a predetermined V_T via a constant or a decelerating inspiratory flow. Flow profiles of appropriate length of inspiratory "holds" or "pauses" are applied as necessary for the desired I:E ratio. Pressure-controlled IRV is more widely used than volume-cycled IRV in patients with ARDS. Since MAP is a major determinant of P_{aO_2}, a major part of the rationale for using IRV in ARDS is to maintain MAP relatively high, but to hold peak alveolar pressure within a safe range. The second theoretic concept underlying IRV is the prolongation of inspiration to allow for recruitment of lung units with long time constants. If air trapping does not develop, MAP will increase without a change in PAP or V_T. On the other hand, if T_I is so prolonged that air trapping does develop, the resulting auto-PEEP will either raise PAP (volume-cycled IRV) or decrease V_T (pressure-limited or pressure-controlled IRV). Indeed, it appears that many of the reported advantages of IRV in improving P_{aO_2} are related to air trapping (auto-PEEP), and that similar beneficial effects on oxygenation or O_2 transport may be obtained by using conventional I:E ratios with sufficient PEEP to obtain the same increase in mean lung volume.[136,137] Deep sedation and/or paralysis are nearly always required. At present, there is a lack of convincing data to support the advantage of IRV over conventional ventilation. To our knowledge, no study has evaluated the outcome or the comparative incidence of pulmonary barotrauma in ARDS patients treated with IRV as opposed to conventional ventilation. Nevertheless, if IRV is used, it can be safely implemented in the critically ill with ARDS, according to the following guidelines:

(i) Volume-controlled IRV may be easier to implement than pressure-controlled IRV since volume-cycled modes are often more familiar to many clinicians. This ventilatory mode guarantees a preset V_T and is available on all ICU ventilators.

(ii) Deep sedation is required in most patients under IRV to avoid dyssynchrony with the ventilator.

(iii) Careful monitoring of PAP and end-inspiratory plateau pressure is required during volume-controlled IRV. The high pressure alarm should be set at 10 cm H_2O above the intended PAP.

(iv) Careful monitoring of $\dot{V}_E$ is required during pressure-controlled IRV because V_T is markedly dependent on the patient's respiratory mechanics.

(v) The auto-PEEP level, which may develop as the I:E ratio increases, should be regularly measured (see Section 4, A-6).

(vi) Hemodynamic status should be assessed using a Swan-Ganz catheter when IRV is implemented.

These guidelines should help minimize the two major complications associated with the use of IRV: pulmonary barotrauma and hemodynamic deterioration.

4. *Airway Pressure Release Ventilation (APRV)*: Airway pressure release ventilation increases alveolar ventilation by intermittently releasing continuous positive pressure generated by the ventilator. In passive patients, APRV is

identical to pressure-controlled IRV; however, the patient's ability to breathe spontaneously during APRV creates a markedly different intrapleural pressure waveform.[90,138] The rationale for APRV is to limit PAPs, thereby limiting barotrauma. APRV is not intended for patients with severe airflow obstruction.

There are two types of pressure release ventilation: APRV during which pressure release time is preset,[139] and IMPRV. Both are specifically designed for assisting spontaneously breathing patients.[90] In these modes, ventilatory assistance is provided by intermittent changes in FRC related to changes in PEEP. Comparative experimental and clinical studies have shown that APRV and IMPRV can improve alveolar ventilation of animals and humans breathing with CPAP, without a deterioration in arterial oxygenation or an increase in PAP.[90,138] When compared with CMV, APRV was shown to produce similar hemodynamic effects at similar MAP in patients with acute respiratory failure.[140] Whether this type of ventilatory support has any advantage over CMV with PEEP in terms of pulmonary barotrauma is not known. APRV can be provided by a CPAP breathing circuit in which the CPAP level can be modified by opening or closing a release valve connected to a timer.

IMPRV, which has been integrated in an ICU ventilator,[90] provides end-expiratory pressure changes according to the patient's spontaneous breathing activity. Respiratory monitoring and alarms are available, and each spontaneous inspiration can be assisted by PS. If the patient's respiratory frequency increases above 30/min, auto-PEEP becomes a limiting factor, and IMPRV is no longer an efficient method of ventilatory support.

During APRV, the following respiratory parameters are preset: upper and lower airway pressure levels, frequency of pressure release, and pressure release time. During IMPRV, the following respiratory parameters are preset: upper and lower PEEP levels, frequency of PEEP changes, and sensitivity of the trigger. Ventilatory assistance is maximum when PEEP is changed in each of two spontaneous respiratory cycles and can be progressively decreased by spacing PEEP changes (PEEP release every 2,3,4,5,6 cycles *etc.* ... spontaneous expiration). Whether this type of ventilatory assistance can facilitate weaning of patients with acute respiratory failure is not known.

Section 7: Discontinuation of Mechanical Ventilation

A. *What Is It, and When Does It Begin?*

Weaning has been defined as the process whereby mechanical ventilation is g*radually* withdrawn and the patient resumes spontaneous breathing.[141] Within the daily vernacular of the ICU, most clinicians do not employ the term weaning in the strict sense, but rather they use it to include the overall process of discontinuing ventilator support. To enhance communication between investigators and clinicians, it may be wise to drop the term *weaning*, and replace it by a term such as discontinuation of mechanical ventilation. This, in turn, could be subdivided into different categories depending on the pace of the discontinuation process—these terms could replace older, less precise terminology such as the "fast wean" and "slow wean." Alternatively, the term *discontinuation* could be used to describe disconnecting the patient from the ventilator over a short, predefined time limit, while *weaning* refers to the more gradual process; unfortunately, the dividing line between these two processes is arbitrary with no obvious basis.

It has become increasingly difficult to define the precise time at which the discontinuation process commences. It was relatively easy to define this time in the past when volume-cycled A/C ventilation and T-tube trials were the sole or predominant method of treating patients. With the widespread use of IMV and PSV in modern ICUs, it has become increasingly difficult to define the precise time at which these modes are no longer being used as the primary mode of ventilator support and are being adjusted to assist with the discontinuation process. In an ICU setting, ventilator support is typically initiated because of an episode of acute respiratory failure. In general, most clinicians would consider it imprudent to start a discontinuation process until there is evidence of significant resolution of the initial precipitating illness. Unfortunately, rigorous physiologic or clinical indices have never been proposed to help to define this time. This largely relates to the lack of data characterizing the changes in respiratory function from the time that ventilator support is instituted until the time that it can be safely withdrawn. Until this time can be defined in clear-cut objective terms, it is going to be extremely difficult to conduct trials comparing the efficacy of different techniques of discontinuing mechanical ventilation.

B. *Relative Importance of Pathophysiologic Determinants of Discontinuation Process*

There are four major factors that determine the ability to discontinue ventilator support: (1) respiratory load and the capacity of the respiratory neuromuscular system to cope with this load; (2) oxygenation; (3) cardiovascular performance; and (4) psychological factors.

To our knowledge, systematic studies have never been conducted to determine the relative importance of these pathophysiologic mechanisms. However, many clinicians and investigators suspect that respiratory muscle dysfunction resulting from an imbalance between respiratory neuromuscular capacity and load is the most important determinant. Unfortunately, measurements of each of the components included in this balance have not been systematically obtained in patients at the time that ventilator support is being discontinued. Measurements of respiratory center output indicate that a depressed respiratory drive is rarely responsible for the inability to discontinue ventilator support.[142,143] Phrenic nerve function is usually satisfactory, except for a small proportion of patients who develop

problems following coronary artery bypass surgery. Respiratory muscle strength is reflected by measurements of maximal inspiratory pressure.[144] Available evidence suggests that this, *on its own*, is not an important determinant of the ability to resume and sustain spontaneous ventilation after a period of mechanical ventilation.[145] A number of techniques can be used to assess respiratory muscle endurance or fatigue in a research laboratory. None of these has ever been reliably applied in ventilator-supported patients. Thus, we do not know if respiratory muscle fatigue ever occurs in patients who are unable to resume spontaneous ventilation and, if it occurs, how important it is in determining clinical outcome or patient treatment. Respiratory muscle fatigue has been defined in dichotomous terms (present or absent), but the impairment in contractility is more likely to exist in the form of a continuum. Thus, it is quite conceivable that "mild fatigue" *per se* may not seriously interfere with the process of discontinuing ventilator support. This is an area where additional research is sorely needed.

The load on the respiratory system is primarily determined by an increase in respiratory resistance, a decrease in respiratory compliance, and the presence of auto-PEEP, which poses an additional threshold load. Each of these factors could produce a marked increase in respiratory work and interfere with the process of discontinuing the ventilator. Although measurements of respiratory work have been obtained in patients at the time of discontinuing mechanical ventilation, most studies contain significant methodologic flaws.[141] Even allowing for these limitations, it is doubtful that a single threshold value of respiratory work can reasonably discriminate between patients who are able to successfully sustain spontaneous ventilation and those requiring continued ventilator support. In particular, there is a tremendous need for research defining the precise interplay between respiratory load and respiratory muscle performance in such patients. Such knowledge would be important not only in elucidating the mechanisms responsible for the inability to resume spontaneous ventilation, but it would also help in guiding optimal ventilator support prior to the discontinuation attempts.

Although mechanical ventilation is commonly instituted because of problems with oxygenation, this is rarely a cause of difficulty at the time that mechanical ventilation is being stopped, largely because ventilator discontinuation is not contemplated in patients who display significant problems with oxygenation.

Research into the discontinuation of ventilator support has primarily focused on factors affecting the respiratory system. Although impaired cardiovascular performance has significant impact on the respiratory system (decreasing O_2 supply to the respiratory muscles, increasing respiratory work secondary to pulmonary edema, and hypoxemia as a result of a low mixed venous O_2 tension), remarkably few studies have examined the role of cardiovascular performance as a determinant of the ability to resume successful spontaneous ventilation.[146] In patients with known coronary artery disease, significant cardiovascular impairment reflected by a marked increase in pulmonary artery occlusion pressure has been documented at the time of resuming spontaneous ventilation. This is another area where much research is required, both in patients who require ventilator support primarily because of cardiovascular problems, and in patients without obvious underlying cardiovascular disease. In particular, it is important to document the time course of significant decompensation in such patients and to determine if this differs significantly from the pattern occurring in patients with a primary pulmonary disorder.

Psychologic factors are a major determinant of outcome in some patients, especially in those patients who require prolonged ventilator support.[147] Minimal research has been conducted into this important issue, and, thus, it is difficult to state its relative importance in determining the ability to resume spontaneous ventilation.

C. *Predictive Indices*

A wide variety of physiologic indices have been proposed to guide the process of discontinuing ventilator support. Traditional indices include the P_{aO_2}/F_{IO_2} ratio, the alveolar-arterial P_{O_2} gradient, maximal inspiratory pressure, VC, $\dot{V}_E$, and maximum voluntary ventilation.[144,145] Newer indices include pressure measured 0.1s after occlusion of the airway, the f/V_T ratio, and integrative indices such as CROP (an integrative index which includes compliance, rate, oxygenation, and pressure[148]), the pressure-time index, and V_E40.[143,148,149] In general, these indices evaluate a patient's ability to sustain spontaneous ventilation. They do not assess a patient's ability to protect his/her upper airway. Indices of upper airway function have been developed for treating postoperative patients, but similar indices have not been evaluated in critically ill patients.

There are enormous discrepancies in the literature on the accuracy of indices in predicting successful discontinuation of mechanical ventilation. Discordance is due, at least in part, to methodologic problems and differences among studies. These include the following: (1) characteristics of the patient population; (2) the method of making the measurements; (3) reproducibility of the measurement; (4) the method of selecting the threshold value of an index; (5) the method of testing the accuracy of an index; and (6) definition of end points in the evaluation study.

As currently employed, predictive indices are most commonly used in evaluating a patient for extubation. Measurement of these physiologic indices may suggest to a physician that ventilator support can be discontinued at an earlier time than he/she might otherwise have thought possible. This may help in decreasing the risk of complications associated with mechanical ventilation. When an index suggests that resumption of sustained spontaneous ventilation is unlikely to be successful, it can provide important information regarding the patient's underlying pathophysiologic state. However, there is no evidence to

suggest that a particular set of physiologic indices is helpful in guiding the selection of a particular technique to hasten the process of discontinuing ventilator support. Accordingly, at this time, it is impossible to say precisely if, and how, such physiologic indices should be used in clinical decision making or in the treatment of a patient who is still requiring ventilator support.

It is important to remember that the condition of ventilator-dependent patients can vary considerably from day to day. Thus, a patient's ability to successfully resume and sustain spontaneous ventilation should be evaluated on a recurrent basis.

D. *Techniques of Discontinuing Ventilator Support*

The major techniques of discontinuing ventilator support include T-tube trials, IMV, and PSV.

There is considerable variation among clinicians in the manner of applying T-tube trials.[141,150] Some clinicians continue maximal ventilator support (*eg*, CMV with neuromuscular blockade or A/C) up until the point at which they believe that a patient has a reasonable chance of extubation. This decision is usually based on clinical examination and measurement of physiologic indices. At this point, the ventilator is stopped, and the patient breathes through a T-tube system. The duration of such a T-tube trial has never been standardized, and it varies from about 30 minutes to several hours. During the trial, a decision is made to extubate the patient (provided that problems with upper airway protection are considered unlikely) or to reinstate ventilator support. Some clinicians do not attempt another T-tube trial for ≥24 h after an unsuccessful attempt. Other clinicians employ intermittent T-tube trials of gradually increasing duration (from 5 to 60 min) intermittently (*eg*, 3 to 4 h apart); this is conducted on an empirical basis.

Intermittent mandatory ventilation was the first alternative approach to T-tube trials.[150,151] IMV involves a gradual reduction in the amount of support being provided by the ventilator and a progressive increase in the amount of respiratory work being performed by the patient. The pace of decreasing the IMV rate is generally based on clinical assessment and measurement of arterial blood gas values, but precise guidelines do not exist. As discussed elsewhere in this consensus conference, breathing through the demand valve of an IMV circuit can produce a marked increase in the work of breathing (see Section 4, B-3).

Pressure support ventilation can also be used to gradually decrease the level of ventilator support.[152-154] The level of PSV is gradually decreased so that a patient becomes increasingly responsible for a larger proportion of overall ventilation. It is commonly assumed that the level of PSV can be decreased to a low level that will compensate for the resistance of the ET tube and circuit, and that the patient can then be extubated at that level of PSV.[108,155,156] Unfortunately, there are no simple parameters that can predict the level of PSV that compensates for this resistance in an individual patient.

A gradual approach to the discontinuation of mechanical ventilation (*ie*, IMV or PSV vs abrupt T-tube trials) has two theoretical advantages: (1) the use of less positive pressure (since these are modes of partial rather than full assistance), and, thus, a potential for fewer pressure-related complications, and (2) performance of some level of respiratory work should prevent the development of respiratory muscle atrophy—this is mainly an advantage when contrasted with a patient receiving CMV with neuromuscular blockade, since patients being treated with A/C (with or without intermittent T-tube trials) probably perform sufficient work to prevent significant deconditioning.

In addition to the independent use of T-tube trials, IMV, or PSV as approaches to discontinuing ventilator support, these techniques are frequently integrated and specific protocols defined for a given patient in an attempt to establish the most optimal approach. That is, PSV and IMV have been combined, with both gradually decreased, or the level of one technique kept constant while the other is gradually decreased. T-tube trials have also been integrated with PSV and IMV.

At the present time and to our knowledge, no study has been published that has compared the optimal use of three major techniques of discontinuing mechanical ventilation.

E. *Treatment of the Difficult Patient*

Discontinuation of mechanical ventilation poses considerable difficulty in a significant proportion of patients. These patients account for a disproportionate amount of healthcare costs, and they pose enormous clinical, economic, and ethical problems. In addition to the factors already discussed, several other issues need to be considered in these patients. Increasing ventilator support at night to ensure maximal rest is recommended. In a recent study, the institution of a ventilator-management team was shown to decrease the number of ventilator and ICU days.[157] Nutritional support needs to be considered since these patients are dependent on a ventilator for a relatively long time. Uncontrolled, retrospective studies suggest that nutritional supplementation can expedite the discontinuation of mechanical ventilation, but this has yet to be examined prospectively.[141] Likewise, respiratory muscle training appeared promising in an uncontrolled study,[158] but its benefit has yet to be evaluated prospectively. Finally, a prospective study of biofeedback was shown to be particularly beneficial.[147] However, skilled practitioners are not widely available, and the initial beneficial findings in this study need to be confirmed.

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RETROSPECTROSCOPE REDUX:

Inflation—1904 Model

When general anesthesia was discovered in 1846,* the practice of surgery exploded in many directions. Previously limited to procedures that the surgeon could complete swiftly with lightning slashing and stitching and that the patient could tolerate with the help of morphine, alcohol, or "biting the bullet," surgeons could now perform a variety of operations that required longer periods of dissection, probing, excision and careful repair.

But this did not include intrathoracic operations. For a variety of reasons,[1] cardiac surgery didn't "take off" until almost 100 years after Morton first demonstrated the use of ether, and pulmonary surgery was still pretty dangerous business until the mid-1930s. The first successful lobectomy in man was performed by Ferdinand Sauerbruch in 1908 and the first successful one-stage pneumonectomy by Evarts Graham in 1933;[2] before 1933 an entire lung had been removed from 2 patients, but in each, the surgeon simply ligated the hilum of the lung and allowed the tissue to slough out!

What held back pulmonary surgery? The main problem seems to have been pneumothorax and inability of the surgeons to cope with it. In 1904, Sauerbruch, the great German surgeon, finally hit Upon a way to prevent it.[3] His reasoning was simple: The lungs normally function in a box, the thoracic cage, where pressure is subatmospheric (negative); this overcomes the elastic recoil of the lungs and keeps them expanded, even at end-expiration. Therefore, to avoid pneumothorax, all one need do is put the *patient* (except for his head) in a box and keep the box at subatmospheric pressure; then when the thorax is opened surgically, atmospheric pressure acting on the patient's nose and mouth outside the chamber will keep the lungs expanded, since the lungs are within the negative pressure chamber.

Sauerbruch first worked with animals and a cuirass-type chamber that enclosed only the dog's thorax; the chamber had 2 sleeve-type openings that permitted him to work with both hands inside it. He then built a larger chamber that enclosed all of the dog (except for its head) and all of the surgeon; the surgeon could now sit in relative comfort and leisurely open the thorax and operate on the lung. Pressure within the chamber was kept at 10 mm Hg less than room pressure and this pressure difference prevented the dreaded pneumothorax.

Sauerbruch was now ready to operate on human lungs. For this, he built a special negative pressure room that could accommodate the patient, the surgeon, and the surgeon's assistants (Figure 1). It even had an antechamber fitted as an air lock so that assistants could enter or leave the main chamber without altering its negative pressure (Figure 2). Sauerbruch's chamber excited the interest of surgeons throughout Europe and thoracic surgeons in Berlin, Cologne, Vienna, St. Petersburg, and other medical centers soon installed this new device. It probably reached the ultimate in size in Willy Meyer's "Universal Negative Pressure Chamber" set up in the Rockefeller Institute in New York City in 1909.[4] One thousand cubic feet in volume, it could contain 17 persons in all: the patient, the surgeon, the surgeon's assistants, visitors, an engineer to maintain the air pressure, and 2 anesthetists; the latter, along with the patient's head, were in a positive

*For practical purposes, 1846 marked the beginning of anesthesia for surgical operations. However, Priestley noted the anesthetic properties of nitrous oxide in 1776 and Davy suggested its use in surgical operations in 1800; Faraday commented on the anesthetic properties of ether in 1818 and Crawford Long used ether anesthesia in 1842 when he excised a patient's tumor (Long did not report his discovery until 1849).

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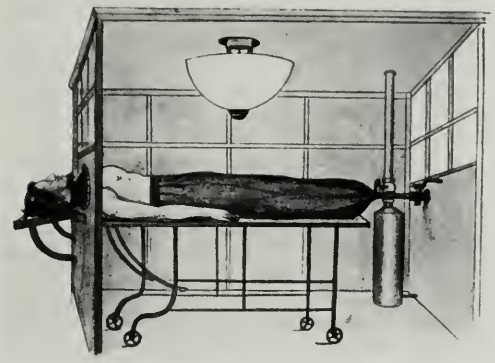

Fig. 1

pressure chamber within the negative pressure room!

Yet, despite the ingenuity and inventiveness of those who conceived these elaborate devices that captured the imagination of the surgical world, no one thought of *ventilation. Inflation* of the lungs, *yes,* but *ventilation,* the process by which fresh air enters alveoli and alveolar air leaves, no. The only goal was to keep the lungs inflated *continuously,* and, at all costs, to prevent even temporary deflation. True, the patient could move his thorax and continue to make respiratory movements. However, the lung in the *open* hemithorax remained motionless (unless air was sucked from it into the other lung during inspiration) and respiratory movements of the lung in the *closed* hemithorax must have been inadequate for the exchange of O_2, and CO_2, considering the handicaps imposed by a mobile mediastinum, deep anesthesia, and further depression of breathing caused by reflexes from fully inflated lungs.

Since every schoolboy or schoolgirl now learns how to maintain ventilation in an apneic person by repeated cycles of blowing into the patient's mouth and then allowing expired air to escape, the negative pressure devices spawned by Sauerbruch in the early 1900s are hard to explain. And they are practically inexplicable when we add that, in 1543, Andreas Vesalius rhythmically ventilated the lungs of a pig;[5] in 1667, Robert Hooke did the same for a dog whose thoracic cage had been completely removed;[6] and throughout the nineteenth century physiologists used bellows and pumps to provide rhythmic

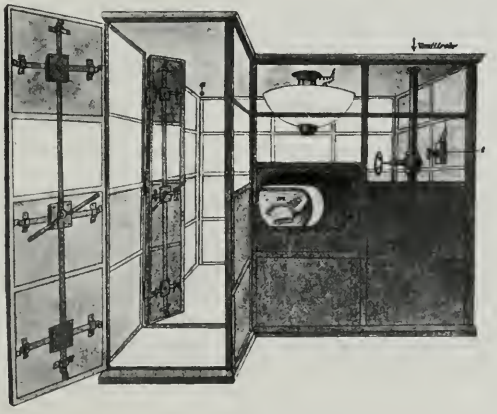

Fig. 2

artificial ventilation for animals employed in laboratory experiments.

If there was little or no communication between physiologists and surgeons in Sauerbruch's time, there should have been more between surgeons and surgeons. In 1899, Rudolph Matas, professor of surgery at Tulane and an eminent thoracic surgeon, wrote in the Annals of Surgery:

> The procedure that promises the most benefit in preventing pulmonary collapse in operations on the chest is the artificial inflation of the lung and the rhythmical maintenance of artificial respiration by a tube in the glottis directly connected with a bellows. Like other discoveries, it is not only elementary in its simplicity, but the fundamental ideas involved in this important suggestion have been lying idle before the eyes of the profession for years. It is curious that surgeons should have failed to apply for so long a time the suggestions of the physiological laboratory, where the bellows and tracheal tubes have been in constant use from the days of Magendie (1783-1855) to the present, in practicing artificial respiration on animals.[7]

In 1893, Fell of Buffalo described an apparatus he devised to maintain artificial respiration in patients with opium poisoning; it was identical to that used in physiological laboratories except that it provided the option of using either a tracheal cannula inserted through a tracheotomy or a mask.[8] O'Dwyer soon eliminated the danger of tracheotomy and the inefficiency of a mask by using an endotracheal tube (devised in 1880 by Macewen[9]). O'Dwyer commented simply, "In the performance of artificial respiration by any means, it is important to remember that all we have to do is to get air into the lungs, and give it sufficient time and room to escape, the power generated and stored up in overcoming the resistance to inspiration being amply sufficient to carry on expiration."[9a] The external end of O'Dwyer's endotracheal tube had 2 branches: one branch conducted fresh air to the lungs from a foot-operated bellows while the operator's thumb closed the other branch; expiration occurred when he removed his thumb. Matas recommended use of the Fell-O'Dwyer apparatus and it was used at least once in 1899 by his associate, Parham, with "brilliant" success, but it never caught on. Quénu and Longuet used an airtight helmet and positive pressure in 1896,[10] and in 1904, Brauer revived the Quénu-type helmet and positive pressure. But both of these techniques used *continuous* positive pressure; only Tuflier and Hallion,[11] working in François-Franck's physiology laboratory, ventilated the lungs rhythmically, but no one except Matas seems to have paid attention to their report.

Today no one uses large negative-pressure chambers for intrathoracic operations. When and why did modern endotracheal rhythmic positive pressure ventilation come about? World War I probably had something to do with the elimination of these cumbersome chambers (except in Germany, where they were still used in the 1930s, so great was the prestige of Sauerbruch), because they were hard to set up near the front lines where they were most needed. The introduction of the Meltzer-Auer technique, far simpler than any other, was also responsible for the decline of the negative pressure chamber, although, curiously enough, it also ignored the matter of gas exchange.[12] This new technique needed no boxes, chambers or special rooms; all it required was an endotracheal tube and a source of compressed air. When the tube filled just enough of the trachea and when the pressure bottle delivered slightly more air to the trachea that initially could flow out between the tube and the tracheal wall, a positive pressure developed in the distal airways and alveoli that kept them continuously inflated when the surgeon opened the thorax. Although Meltzer and Auer's opening sentence was, "The object of the function of respiration is to supply the animal with oxygen and to remove carbon dioxide," they never measured blood O_2, or CO_2 and, because their dogs recovered, simply took it for granted that "under these conditions the supply of oxygen and removal of carbon dioxide take place apparently in physiological fashion."

Rhythmic inflation of the lungs gradually replaced continuous distention. Crafoord[13] credits his former chief, KH Giertz, with demonstrating in 1914-1916 that (1) there was no essential difference in pulmonary ventilation accomplished by negative versus positive pressure and (2) rhythmic insufflation during inspiration followed by free outflow during expiration was clearly superior to all other methods of managing ventilation and preventing pneumothorax during operations on the lungs. Other factors were the introduction of direct-vision laryngoscope by Chevalier Jackson, which made it far easier for non-experts to insert an endotracheal tube;[14] the invention of the first closed-circuit anesthesia apparatus by Dennis Jackson,[15] who designed it to recycle expensive anesthetic gases and so reduce the cost of anesthesia to the poor; the introduction of a simple to-and-fro closed-circuit rebreathing system by Ralph Waters;[16] the change-over from clinical anesthesia to academic anesthesiology with a strong research component; the intro-

duction of rapid or even continuous methods for measuring O_2, and CO_2 in blood and air; and the demonstration by Dripps[17] and by Beecher and Murphy[18] of harmful effects of CO_2 accumulation during anesthesia, even when hypoxia was prevented by supplying high concentrations of O_2 to the patient.

What lessons can we learn by using the Retrospectroscope to look at this curious era of the negative pressure chamber? Several: (1) Scientists and clinicians usually advance but sometimes retard progress. (2) An impressive piece of hardware, backed by a highly prestigious designer, can hold back progress for decades. (3) It was difficult for surgeons to understand (a) that a transpulmonary pressure difference of 770 minus 760 mm Hg inflated the lungs the same amount as one of 760 minus 750 and (b) that because diffusion over long distances is a very slow process, adequate gas exchange requires alveolar ventilation. (4) A trip—in either direction—across the street that separated basic science (physics or physiology in this case) from clinical departments could have accelerated the advent ot successfull pulmonary surgery by at least 50 years. (5) Finally, what are we, with our infinite wisdom and magnificent technical advances. doing today that will appear primitive, curious, or even stupid 50 years from now?

JULIUS H. COMROE, JR.

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Radiographic Findings in a Blunt Trauma Patient

Grace Nadell BS and Frederick W Clevenger MD

An 85-year-old woman was a passenger in a car that was struck by a pick-up truck in a 'T-bone' (broadside) collision at an intersection. She sustained blunt injuries to her chest and abdomen and multiple fractures to her lower extremities. She was alert and oriented immediately after the accident, and was placed on a long spine board for immobilization. The patient arrived at the emergency room complaining of chest and right-leg pain. She was transferred to the regional trauma center and soon developed mild respiratory distress. Her blood pressure was 175/85 and her heart rate 88. She was mildly tachypneic with a respiratory rate of 28. Physical examination revealed no breath sounds in the left lung base. An upper-abdominal contusion was apparent, and presumed to have been caused by the lap belt; the abdomen was moderately tender to palpation. Because of the trauma to the abdomen, a diagnostic peritoneal lavage was performed but showed no evidence of intra-abdominal bleeding. Cervical-spine films were normal. The chest radiograph taken at admission is shown in Figure 1.

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Fig. 1. Portable anteroposterior (AP) chest radiograph taken shortly after patient's admission to the trauma center.

How would you answer these questions?

What radiographic abnormalities are present?

What pathologic process(es) could explain these findings?

What tests are required to establish the diagnosis?

What action or therapy is indicated?

Answers and Discussion on next page

Answers

Radiographic Findings: The chest radiograph in Figure 1 is annotated for Figure 2. It shows the nasogastric tube in the left chest—strong diagnostic evidence for rupture of the left diaphragm. The outline of the stomach can be seen just above the tip of the nasogastric tube. Because the nasogastric tube is not evident within the left main-stem bronchus but rather courses below the diaphragm before entering the chest, it is clear that it has not entered the chest cavity by penetration of the lung parenchyma. Also evident on the admission chest radiograph are (1) rightward deviation of the trachea, (2) a widened mediastinum, and (3) an ill-defined left aortic contour. The differential diagnoses for this triad of findings include compression of the lung parenchyma by a diaphragmatic hernia and possible aortic rupture.

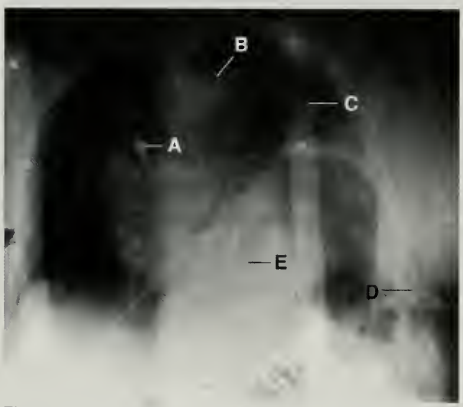

Fig. 2. This copy of Figure 1 is annotated to show (a) zipper, (b) calcification of the aorta, (c) backboard artifact, (d) one of the many lower lateral rib fractures on the left side, and (e) bra clasps. Obviously, this patient's clothing had not yet been removed. Note that the film is hyperlucent on the right compared to the left, but this does not represent a pneumothorax. Indeed it represents consolidation of lung and abdominal viscera in the left chest, creating a more dense appearance throughout the left hemithorax as compared to the right.

Diagnostic Confirmation: The position of the nasogastric tube in the left chest is diagnostic for a diaphragmatic hernia. No further diagnostic tests are required. Diagnostic confirmation of a ruptured aorta is best accomplished by aortography. Given the mechanism of the injury, we were concerned that the patient may have sustained an aortic rupture. However she was hemodynamically stable and we decided to proceed with exploratory laparotomy and then perform aortography if the radiographic abnormality (widened mediastinum) persisted after reduction of the diaphragmatic hernia.

Clearly the consequences of missing a blunt aortic rupture are severe. Blunt aortic injury if initially survived carries a 50% per day mortality such that by the end of a 1-week period of time, few of those who initially survive are alive due to late delayed rupture. However, because the findings suspicious for aortic rupture (deviation of the nasogastric tube to the right, wide mediastinum, indistinct aortic knob, right apical capping, and tracheal deviation to the right) are also seen in patients with left diaphragmatic hernia and evisceration, a decision was made to treat the known pathology prior to investigation of what could prove to be a spurious set of x-ray findings. Because the only way to definitively diagnose blunt aortic rupture is aortography, and because aortography would carry significant morbidity in a patient of this age who had just experienced severe trauma, we chose to treat the identified pathology first and see if subsequently the chest radiograph finding resolved.

Action or Therapy: Repair of a diaphragmatic tear should be initiated as soon as possible because of the risk of rapid cardiopulmonary deterioration.[1] The primary surgical approach is via laparotomy given the high incidence of associated intra-abdominal injuries.[2-7] A transthoracic approach is indicated to repair rupture of the right hemidiaphragm if it appears that the liver may prevent access using the abdominal approach. Thoracotomy also facilitates freeing of adhesions between bowel and lung parenchyma that occur in cases where the diagnosis of traumatic diaphragmatic rupture (TDR) is delayed.[3,5,8-11]

Exploratory laparotomy in this case revealed a large diaphragmatic tear extending posteriorly from the most lateral portion of the diaphragm to the gastroesophageal junction. The stomach and a portion of the small and large bowel within the chest cavity were reduced to the abdominal cavity and the diaphragmatic tear closed with running O-prolene su-

ture. A 3-cm injury to the wall of the stomach and three small spleen lacerations were also repaired. The postoperative radiograph in Figure 3 shows a clear mediastinum of normal width and correct placement of the nasogastric tube below the surgically repaired left hemidiaphragm. Unfortunately, the patient could not be weaned from ventilatory support after surgery. Multiple organ failure ensued, and life support was gradually withdrawn in accordance with the patient's living will and the wishes of the family.

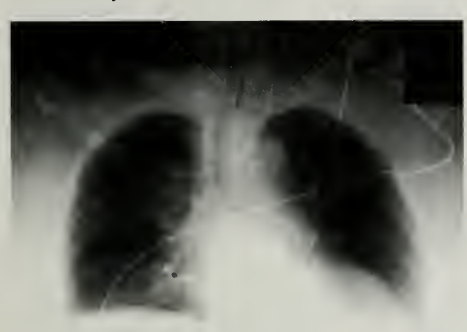

Fig. 3. Portable AP chest radiograph taken after surgical repair of a traumatic diaphragmatic hernia. Note resolution of the widened mediastinum and correct placement of the nasogastric tube below the normally positioned left hemidiaphragm.

Discussion

Blunt trauma secondary to motor vehicle accidents is the most common cause of diaphragmatic rupture.[9,12-14] The incidence of diaphragmatic rupture ranges from 0.1 to 3% of patients surviving severe blunt trauma.[1,6,10,15] During severe blunt trauma, a sudden increase in intra-abdominal pressure transmits enough force to rupture the diaphragm. Such trauma generally causes large (> 10 cm) radial tears.[1,4,16] Visceral herniation into the chest cavity occurs as a result of the difference between the negative intrapleural pressure and the positive intra-abdominal pressure established during respiration. The most commonly herniated organ in left-hemidiaphragm rupture is the stomach,[3,6,10] although colon, spleen, small bowel,[17,18] and omentum[4,9,11,19] may also be involved. The liver most commonly herniates in cases in which the right hemidiaphragm is ruptured.[19]

The majority of diaphragmatic injuries occur on the left, presumably due to the cushioning effect of the liver on the right diaphragm.[5,17,20] Although tears can occur anywhere, the posterolateral portion of the left diaphragm is most frequently affected.[5,11,14] This corresponds to an embryologically weak area called the lumbocostal trigone and is the transition zone in the diaphragm between the lateral rib cage and where the diaphragm attaches to the back.[8]

The pathophysiologic effects of TDR on circulatory and respiratory status are due to impaired diaphragmatic function and compression of lung tissue by herniated viscera that result in decreased alveolar ventilation. Mediastinal displacement, also caused by compression, can interfere with venous return to the heart.[2] In rare instances, visceral herniation into the pericardial sac may lead to cardiac tamponade.[3] Clinical findings are often nonspecific and may be masked by the presence of other life-threatening injuries. The most common symptoms are chest pain and dyspnea due to the effects of abdominal viscera in the chest cavity.[2,9] Bowel sounds audible in the chest are pathognomonic for diaphragmatic hernia. Other physical findings include hypotension, absent breath sounds, and hypertympany or hypotympany of the left chest. If large amounts of the abdominal viscera are herniated into the chest, a scaphoid abdomen may be noted.

Diaphragmatic rupture rarely occurs as an isolated finding because the extreme force required to rupture the diaphragm is nearly always associated with severe trauma that affects other organ systems. Intra-abdominal injuries are most commonly associated with TDR and can include rupture of the spleen, liver, and kidneys.[2,4,17,19] Chest injuries include lung contusion or laceration, hemothorax, and pneumothorax.[4,17] Severe flail chest suggests a diaphragmatic hernia until proven otherwise.[2] Fractures of the ribs, pelvis, and long bones[4,17,21] are also frequently associated.

Often the diagnosis of traumatic diaphragmatic rupture is missed.[1-6] Patients may present months or even years after the traumatic event with signs and symptoms of gastrointestinal obstruction or strangulation. Complications from delayed diagnosis are responsible for most of the morbidity and mortality associated with diaphragmatic rupture.[13,19] There-

fore, the importance of prompt and accurate diagnosis of TDR cannot be overemphasized. It is important to keep in mind that positive pressure ventilation can mask a diaphragmatic hernia by preventing or limiting herniation of abdominal contents into the chest cavity. For this reason, the chest radiograph must be repeated after a patient with a history of blunt trauma has been taken off the ventilator.[17] The appearance of a poorly defined left or right hemidiaphragm immediately after positive pressure is discontinued suggests herniation as a result of the newly established pressure gradients.

The most useful diagnostic aid is the chest radiograph. Radiologic signs diagnostic of diaphragmatic rupture are air- or fluid-containing viscera in the left or right chest and a nasogastric tube that terminates in the left lung field.[5,16,18,22] TDR should be suspected if the diaphragm is elevated, indistinct, or irregular.[4,14] Opacities within the pleural cavity or a shifted mediastinum may also suggest TDR.[2,7-9,18] Misinterpretation of the chest radiograph causes diagnostic errors that may include hemothorax, pneumothorax, atelectasis, pulmonary contusion, and an elevated hemidiaphragm due to phrenic nerve paralysis.[2] In the absence of a definitive diagnosis, serial chest radiographs may confirm the diagnosis.

A delay in diagnosis or misdiagnosis is a frequent occurrence due to misinterpretation of the chest radiograph. Gelman et al[16] found chest radiographs to be diagnostic of left-sided rupture in 46% of patients and suggestive of the diagnosis in another 18%. When examined retrospectively, however, an additional 18% of cases not diagnosed initially were found to be diagnostic or strongly suggestive of TDR. Clearly, careful assessment of the initial radiograph is vital to establishing a correct diagnosis.

When clinical and radiographic findings are equivocal, exploratory laparotomy has proven to be the most reliable method for diagnosing a diaphragmatic tear.[1] It is important to thoroughly inspect both leaves of the diaphragm during laparotomy because bilateral or multiple unilateral ruptures are possible. Though peritoneal lavage is highly sensitive in assessing abdominal trauma, it is unreliable in diagnosing diaphragmatic injury. A positive lavage may result from associated intra-abdominal injuries and thus is nonspecific for diaphragm rupture.[21] A falsely negative lavage may result from insignificant bleeding from the tear because the torn diaphragm frequently does not bleed. Further, herniation of injured organs into the chest may prevent bleeding into the peritoneal cavity.[11,14,23] In patients, with a negative peritoneal lavage and a suspicious chest radiograph, injection of contrast media or air through the lavage catheter can help confirm the diagnosis.[4,5,8,14,16,21] Variable success has been reported with the use of computed tomography.[5,13,16,18,20,22] Although experience with magnetic resonance imaging is limited, its advantage over computed tomography is its ability to image the coronal and sagittal planes.[16,18] Barium contrast studies of the upper and lower gastrointestinal tract depend on herniated viscera and are most useful in delayed presentation of traumatic diaphragmatic hernia.[13] Liver and spleen scans are useful in the diagnosis of right-side diaphragmatic hernia.[8,13,14,24]

The clinical and radiographic diagnosis of TDR is much more obvious in the presence of herniated abdominal viscera. However, many patients with TDR do not present with herniation and their chest radiograph may be normal or minimally abnormal. It must be kept in mind that any patient who has sustained severe blunt trauma to the thorax and abdomen may suffer a diaphragmatic rupture. A history of blunt trauma should cause the clinician to suspect TDR. Careful interpretation of the initial chest radiograph is required to accurately and promptly identify traumatic diaphragm rupture.

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Letters

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Eagle Eye but 'Picky'—Analysis of Pilbeam Book Review

While reading my August 1993 issue of RESPIRATORY CARE, I was drawn to a review[1] of Sue Pilbeam's book[2] on mechanical ventilation.* The review proved to be lengthy, complete, thorough, and meticulous. However, I also found it to be 'picky,' opinionated, and insular—the latter most inexcusable in a national publication (ie, if we do not like it 'at our place' you should not like it wherever you are).

To avoid making my critique too long, I decided to tabulate the number of type inches of review devoted to each of five categories:

1. Reviewer opinion—23.0 in.
2. Picky interpretation of words—6.5 in.
3. Reviewer wrong (in my opinion)—12.5 in.
4. Insignificant or typographical error—2.0 in.
5. Errors important for reader understanding—6.5 in.

I make that 42 inches that you did not need to hear that much about to 8.5 inches of information critical to you as a reader.

Let me elaborate on Categories 2, 3, and 5.

Category 2. After the reviewer has written "the mistakes start to appear," the review becomes liberally sprinkled with terms such as "seems misplaced," "makes the section confusing," "found inclusion distracting," "would seem more logical," "I believe it would be more correct," "is technically more correct," "we really don't like nasotracheal tubes," "it was disappointing," "however, I believe," "I believe this should read," and "I could take issue with." Because the efficacy of specific mechanical ventilation devices has been so poorly documented in large-scale studies, discussion and dissension is certainly invited, but pickiness should be avoided in professional reviews as well as local preferences. The lengthy discussion of nasotracheal tubes is an example. However, the award for 'pickiness' goes to the 3-inch discussion of a tidal volume range quoted as "10-2500 mL" rather than "10-2000 mL."

Category 3. I believe that the reviewer is wrong on these points:

—IMV definition is mistakenly said to be incorrect due to omission of the phrase "breaths can be pressure controlled." In fact, only ventilators with SIMV can provide pressure control (semantics).

—Similar reasoning prompted a 3-inch dissertation on PR2s, Mark 7s, and iron lungs, which I believe to be incorrect.

—The determination of tubing compliance is deemed wrong because of the use of peak pressure rather than plateau pressure. The reviewer confuses static compliance determinations with tubing compliance corrections to tidal volume.

—An error attributed to Appendix K follows the erroneous line of thought that the Appendix is for correction of tidal volume readings when it actually is for calculation of static compliance.

Category 5. I believe that the reviewer is correct and that the following are important errors:

—Step 2 of Chatburn's ventilator classification should say "stay constant" rather than "change."

—In Appendix A, the calculation of alveolar ventilation incorrectly defines alveolar volume and carries the mistake into the equation.

—On Page 344, a mistake involving "more than" in place of "no more than" changes all meaning in the section, a small but important deletion.

—On Page 72, the answer to Question 5 is miscalculated.

—On Page 288, the incorrect calculated frequency is given in Example 2 (the P_{CO_2} entered in the formula is wrong).

—In Question 3, Page 465, 18 cm H_2O is converted to 24.48 mm Hg (multiplied by 1.36, rather than divided by).

—The answer to Question 16, Page 598 should be d (not c). (Actually, I disagree with both and think it should be e.)

All in all, not a bad record, in my opinion, for a 644-page book of complicated machines, formulas, and calculations.

In summary, I hope Ms Pilbeam can get Ms Piedalue to proofread her next edition—but no review!

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Ms Piedalue responds:

Dr Hunt's letter clearly indicates that he believes that Susan Pilbeam's book on mechanical ventilation deserved a better review. While I admire his efforts to stand up for his be-

*Editors note: This is not a single author book; Sue Pilbeam was editor and contributor along with 5 other contributors.

liefs, I do not believe that his statements are supported by facts or references.

Any medical book written as a standard reference should always be subjected to intense scrutiny. Errors must be recognized and corrected. Failure to do this results in the perpetuation of erroneous thought and application. Ms Pilbeam's book is a victim of the failure of this process. For example, the explanation of the expiratory time limit of the BEAR CUB in her book is incorrect. However, if one researches her reference,[1] it mirrors her book's statements. Only further investigation, the operation manual,[2] yields true accuracy.

Dr Hunt's comment about local preferences highlights one of the points of the review. Local preferences should not be stated as fact. It is the textbook, not the review, that gives local preference as fact. This was the point of the discussion on nasotracheal tubes that somehow Dr Hunt is misinterpreting. It is the book that is saying you must do it our way or you are wrong, not the review.

As far as the "award for pickiness" that he gives for a "3-inch discussion on tidal volume range"—no such discussion exists in the review. He is most likely referring to the example where the Newport E100i is used to illustrate the problems with the appendix. Many of the specifications of the Newport E100i were listed in error. Tidal volume range was only one of them.

Regarding Category 3 where he "believes" that I am wrong—where are his references? I am not wrong on the IMV definition,[3] PR2s,[4] iron lungs,[5] and tubing compliance.[6] The statement that only ventilators with SIMV can provide pressure control is untrue. During my initial years in respiratory care, the PR2 was the ventilator used in our emergency and recovery rooms. When the PR2 was set at pressures $\geq$ 35 cm H_2O it would not flow-cycle off.[4] Hence, when we set a rate on our apneic patients they were on pressure-limited and time-cycled ventilation.[3]

The error in Appendix K is as written in the review.[7] The erroneous line of thought on compliance is in his letter, not the review.

I agree that the review was long, but the book contains 644 pages. Ironically, not only did I not list all the mistakes I encountered but I also shortened the original draft. I tried to support my overall impression of the text with the most important examples.

I believe that Susan Pilbeam is an excellent author who is on the road to creating a classic textbook on mechanical ventilation. However, objective criticism is crucial in developing any tool that is to be used as a standard in our profession. I am confident that her next edition will reach that goal.

Because some of my references are from Robert Chatburn, I would like to borrow one of 'his' quotes he borrowed from Thomas Jefferson:[5]

> Error of opinion may be tolerated where reason is left free to combat it.
>
> *Thomas Jefferson (1743-1826)*

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Pressure Controller and Pressure-Controlled Ventilation

In the book review[1] of "Mechanical Ventilation: Physiological and Clinical Application, 2nd ed," by Susan P Pilbeam, the reviewer Ms Fran Piedalue has made statements that may promote confusion related to proper classification of mechanical ventilators and modes of ventilation. Ms Piedalue, in her criticism of the author's claim that pressure-controlled ventilation gained popularity in the late 1980s, states, "I believe it would be more correct to state that this mode regained popularity. What about those patients ventilated with Bird and Bennett PR ventilators—not to mention the iron lung?" Later on Ms Piedalue claims that pressure-controlled ventilation was used in the 60s and 70s with PR-2s and Bird Mark 7s and 14s.

It appears that confusion exists in the minds of many respiratory therapists about the ventilation delivered by ventilators that are pressure controllers and by the newer mode, pressure-controlled ventilation.

Chatburn has done an excellent job of addressing the issue of ventilator classification.[3] The Bird Mark 7s and 8s are termed pressure controllers where inspiration is terminated as soon as the preset pressure matches the airway pressure; or, according to Chatburn,[4] pressure is considered to be an independent variable.

On the other hand, during pressure-controlled ventilation the venti-

lator is set to terminate inspiration when the preset inspiratory time interval elapses (time cycled). In Chatburn's terms, again, pressure is an independent variable. It is true that pressure is an independent variable in both systems, reflecting a similarity between the two systems. However, the contrast in clinical applications and the cycling mechanism is so profound that these two systems should not be even considered as comparable. Just imagine a novice therapist's suggesting the use of a Bird Mark 7 to provide pressure-controlled ventilation for an ARDS patient.

The ventilation delivered by the Bird Mark 7 can be described as pressure or time-triggered, pressure-cycled ventilation, whereas that during pressure-controlled ventilation is pressure or time-triggered, pressure-limited, pressure-controlled, time-cycled ventilation.[5]

As described and referenced, by Pilbeam,[2] pressure-controlled ventilation is primarily used clinically in critical conditions where lung mechanics are severely compromised and time-cycled, pressure-controlled ventilation is required. On the other hand, the Bird Mark 7 has been employed to deliver pressure-cycled ventilation since its inception and lately its use has been limited to hyperinflation therapy.

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Ms Piedalue responds:

Mr Deshpande raises some very important points in his letter that I would like to clarify.

He describes pressure-controlled ventilation (PCV) as "pressure or time-triggered, pressure-limited, pressure-controlled, time-cycled ventilation." Because the Bennett PR-2 and the Bird Mark 14 can function according to that definition, there should be no disagreement regarding the point made in my review. In addition this also proves that pressure-control ventilation is definitely not a new 'mode' of ventilation as Mr Deshpande suggests. In fact, if one reviews the Chatburn classification system for ventilation modes, PCV is not even considered a mode of ventilator operation.[1] What is new is the current popularity of using a ventilator pressure-controlled breath to treat the adult patient with ARDS.

Mr Deshpande's real concern is obviously my allusion to the Bird Mark 7's functioning as a pressure-controlled ventilator. Because the only variable the Bird Mark 7 controls during inspiration is pressure, it can only be a pressure controller. The issue then becomes whether a machine that is a pressure controller (like the iron lung) can do pressure-control ventilation. Mr Deshpande writes that a pressure controller cannot do pressure-controlled ventilation. I believe this is oxymoronic.

In contrasting the Bird Mark 7 with newer ventilators, Mr Deshpande correctly explains that the cycling mechanism is different—inspiration is over when a set pressure is reached rather than a set time. However, both machines are controlling pressure, and tidal volume varies with system compliance.

What is most important with any ventilator system is to describe precisely how a ventilator breath is delivered because that determines the ventilator's application. It is true that the Bird Mark 7 is now used only for hyperinflation therapy and no longer for continuous ventilation due to its cycling mechanism and other limitations. However, I do not believe that any student—on the basis of the technical description alone—would reach for a Bird Mark 7 for an ARDS patient today anymore than a therapist would attempt to place that same patient on a PR-2.

The real controversy raised by this letter may be whether the manufacturer's label of a 'mode' of ventilation or the popular definition of a mode of ventilation fits a logical ventilator classification system.

For example, consider the mode Volume Control on the Servo 900C. The strict definition of control (ie, the patient cannot trigger a breath) does not apply. When we place a patient on this setting we correctly call the mode assist/control. In fact, the Servo 900C does not technically control volume in this setting. Fortunately, our profession does not define volume Control by what the Servo 900C does in this setting.

Interestingly, however, the current popular 'mode' pressure-controlled ventilation is precisely defined by what the Servo 900C does when placed in the Pressure Control setting. Yet this is the same type of ventilation used routinely with neonates but termed intermittent mandatory ventilation (IMV).

To understand the Servo 900C and how it functions when set in Volume Control we describe the mode as assist/control. The breath delivered is flow controlled and time cycled. When the Servo 900C is set in Pres-

sure Control, we describe the mode as assist/control and the breath delivery as pressure-limited time-cycled ventilation.

The Chatburn classification system uses PCV as a term to describe how ventilator breaths are delivered in a designated mode (eg, assist-control, AC or IMV). As Mr Deshpande writes, he limits this descriptive term to a strict definition of pressure-limited time-cycled ventilation.[1] I believe this is where some confusion may lie. Again I raise the question how can a pressure controller not provide pressure-controlled ventilation? If pressure-controlled ventilation is merely a descriptive term that describes how a ventilator breath is controlled, shouldn't it be allowed to say what it means (ie, ventilation that is pressure controlled)? Further definitions of phase variables define the application and clarify ventilator operation.

This, however logical, runs contrary to the current line of thought—PCV is a "new mode" that is defined by how the Servo 900C performs it. I believe this could be an example of a ventilator classification system developed around a specific ventilator rather than ventilator performance described by a logical ventilator classification scheme.

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Appreciation of Reviewers

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Pharmacologic approaches to respiratory failure [Hudson] **38(7):754** *conference proceedings*

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Comparison between conventional cap and one-way valve in the decannulation of patients with long-term tracheostomies [Le et al] **38(11):1161** *research article*

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HIV, AIDS, & the respiratory care practitioner [Luce] **38(2):189** *lecture*

The re-emergence of tuberculosis: a previously forgotten disease becomes a problem for caregivers [Volosky & Ruben] **38(8):880** *editorial*

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The American Respiratory Care Foundation Announces Literary Awards for 1993

Dr Allen DeVilbiss Award

Best paper published from November 1992 through October 1993 that addresses new technology or a new application of current technology in respiratory care ($2,000 cash plus travel expenses to the AARC Annual Meeting to receive the award)

Choice of Mechanical Ventilator: Influence on Nebulizer Performance—Michael McPeck BS RRT, Thomas G O'Riordan MB, and Gerald C Smaldone MD PhD [Respir Care 1993;38(8):887-895]

1993 Allen & Hanburys Award

Best Original Paper Accepted for Publication from November 1992 through October 1993 ($2,000)

Comparison of Nebulizer Delivery Methods through a Neonatal Endotracheal Tube: A Bench Study—Joseph L Rau Jr PhD RRT and Robert J Harwood MSA RRT [Respir Care 1993;37(11):1233-1240]

4 Papers Based on any OPEN FORUM Presentation ($1,000)

(1) Analysis of an Endotracheal Intubation Service Provided by Respiratory Care Practitioners—Janice J Thalman BS RRT, Susan Rinaldo-Gallo MEd RRT, and Neil R MacIntyre MD [Respir Care 1993;38(5):469-473]

(2) Evaluation of the Agreement between Portable Peak Flow Meters and a Calibrated Pneumotachometer—Mark Simmons MSEd RPFT RRT, Tiffany Wynegar BS CRTT, and Dean Hess MEd RRT [Respir Care 1993;38(8):916-922]

(3) Capnometry in the Surgical ICU: An Analysis of the Arterial-to-End-Tidal Carbon Dioxide Difference—John M Graybeal CRTT and Garfield B Russell MD [Respir Care 1993;38(8):923-928]

(4) Cyanosis and Sulfhemoglobinemia: A Case Report—James M O'Connor BA RPFT RPsgT RRT [Respir Care 1993;38(10):1088-1091]

Best Papers Submitted by 1993 OPEN FORUM Participants Who Have Never Published as First Author ($500)

(1) Interruption of Oxygen Therapy during Intra-Hospital Transport of Non-ICU Patients—Celeste R Stubbs RRT, Karen J Crogan RRT, and David J Pierson MD

(2) An In Vitro Comparison of 3 Methods of Metered Dose Bronchodilator Delivery To Intubated Adults Receiving Mechanical Ventilation—Robert Harwood MSA RRT, Joseph L Rau Jr PhD RRT, and Lynda Thomas-Goodfellow MBA RRT

(3) Rebreathing Technique for Performing Xenon Lung Scans on Intubated Patients—Howard C McDonald Jr RCP, Bahram Redjaee MD, and William Higgins

(4) Comparison of Pressure Support and Pressure Support with Flow-By Combination Using a Weaning Protocol in the Cardiovascular Recovery Room—Hernando Mesina RRT, Doug Sabau RRT, Wadie Williams RRT, Elizabeth Bearden RRT, Joy Kraus-Hargett RRT, and John Sabo RRT

Radiometer Awards for Best Features

PFT Corner #49—Noise or Upper Airway Disorder?—Franklin H Dennison MEd RPFT RRT, Arthur A Taft MHS RRT, and Bashir A Chaudhary MD [Respir Care 1993;38(2):202-206]

PFT Corner #50—Is It Really Asthma?—Sandra E King AS RRT, Pamela Leisenring AS RRT, and Robert H Warren MD [Respir Care 1993;38(5):538-541]

Test Your Radiologic Skill—Left Shoulder, Neck, and Chest Pain with Dyspnea and Nonproductive Cough—C Worth Brooks Jr BS RRT and Shelley C Mishoe MEd RRT [Respir Care 1993;38(11):1201-1204]

Not-for-profit organizations are offered a free advertisement of up to eight lines to appear, on a space-available basis, in Calendar of Events in RESPIRATORY CARE. Ads for other meetings are priced at $5.50 per line and require an insertion order. Deadline is the 20th of the month two months preceding the month in which you wish the ad to run. Submit copy and insertion orders to Calendar of Events, RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593.

Calendar of Events

AARC & AFFILIATES

February 22-25, 1994 in Reno, Nevada. The NSRC and the American Lung Association of Nevada present the 13th Annual High Sierra Critical Care Conference at the Peppermill Hotel Casino. The four-day conference presents critical care topics covering adult, pediatric, and neonatal issues. Contact: Colleen Banghart, American Lung Association of Nevada, PO Box 7056, Reno NV 89510. (702) 829-5864 (9 am to 3 pm PST).

OTHER MEETINGS

January 28-29, Amelia Island, Florida. Assessment and Treatment of Tracheotomy-Tube and Ventilator-Dependent Persons: A Transdisciplinary Team Approach. Contact National Rehabilitation Services, (517) 732-3866 or write NRS, PO Box 1247, Gaylord MI 49735.

February 17, Baltimore Maryland. The Johns Hopkins Hospital Department of Respiratory Care presents a seminar on Respiratory Care and topics in Critical Care Medicine. Includeing Management of Pediatric Trauma Patients, ECMO and Nitric Oxide Therapy, Intra-arterial Blood-Gas Monitoring, Pressure and Volume Ventilation Techniques, and Mechanical Ventilation Techniques in Managing Asthma and Adult Respiratory Distress Syndrome. AARC Category I CRCEs have been applied for. Contact Tony Bilenki RRT at (410) 955-9277.

February 24-25, Omaha, Nebraska. Clarkson College, Division of Professional Development and Clarkson Hospital Department of Pulmonary Medicine present the Third Annual Omaha Regional Pulmonary Symposium. Topics include managed competition, case management, writing critical pathways, ARDS, advances in oximetry and capnography, lung transplantation, and depression in chronic illness. National speakers include Art Vall-Spinosa MD and Penny Tice RN MSN. Other speakers include local and regional experts in pulmonary care. Contact Clarkson College at 800-647-5500 or (402) 552-3039 to receive a brochure.

March 5-8, 1994 in Glasgow, Scotland. The International Congress on Smoking Cessation. For further information, please contact: Jane Fensome, Congress Secretariat, Gardiner-Caldwell Communications Ltd, The Old Ribbon Mill, Pitt Street, Macclesfield, Cheshire SK11 7PT, UK. Tel: 44 625 615325. Fax: 44 625 616563.

March 24-26, 1994 in Helena, Montana. 13th Annual Big Sky Pulmonary Ski Conference. Contact: The American Lung Association of Montana, 825 Helena Ave, Helena MT 59601, (406) 442-6556, fax (406) 442-2346.

April 5-11, Miami, Florida. The 1994 session of Miami Children's Hospital's Annual VACC Camp for ventilation-assisted children and their families will be held. Application due date is Jan. 5, 1994. This community-based, free camp program provides recreation and social support for children with trachs, vents, CPAP, etc., and their moms, dads, and siblings at least five years old. Technology-dependent children should have normal cognitive potential. Contact: Director Moises Simpser, MD, or Program Coordinator Cathy Klein, Ventilation Assisted Children's Center, Division of Pulmonology, Miami Children's Hospital, 3200 SW 60th Court, Suite 203, Miami FL 33155-4076, (305) 662-VACC.

April 21-22, 1994, San Diego, California. Round-Up your rehab skills by attending the California Society for Pulmonary Rehabilitation's 5th Annual Educational Seminar at the beautiful U.S. Grand Hotel. Speakers discuss exercise and nutrition, osteoporosis, ethical issues, allergy and environmental control, depression in COPD, and much more. Also join us for a country/western reception and dance. For more information, contact Mary Jo Goldzimer RN RCP, (619) 759-1513 or Ann Devine BS RRT (909) 884-6673.

1994 Call for Abstracts

RESPIRATORY CARE • OPEN FORUM

The American Association for Respiratory Care and its science journal, RESPIRATORY CARE, invite submission of brief abstracts related to any aspect of cardiorespiratory care. The abstracts will be reviewed, and selected authors will be invited to present papers at the OPEN FORUM during the AARC Annual Meeting in Las Vegas, Nevada, December 10-13, 1994. Accepted abstracts will be published in the November 1994 issue of RESPIRATORY CARE. Membership in the AARC is not necessary for participation.

SPECIFICATIONS—READ CAREFULLY!

An abstract may report (1) an **original study,** (2) the **evaluation of a method or device,** or (3) a **case or case series.** Topics may be aspects of adult acute care, continuing care/ rehabilitation, perinatology/pediatrics, cardiopulmonary technology, health occupations education, or management of personnel and health-care delivery. The abstract may have been presented previously at a local or regional—but not national—meeting and should not have been published previously in a national journal. The abstract will be the only evidence by which the reviewers can decide whether the author should be invited to present a paper at the OPEN FORUM. Therefore, *the abstract must provide all important data, findings, and conclusions.* Give specific information. Do not write such general statements as "Results will be presented" or "Significance will be discussed."

Essential Content Elements

An **original study** abstract *must* include (1) Introduction: statement of research problem, question, or hypothesis; (2) Method: description of research design and conduct in sufficient detail to permit judgment of validity; (3) Results: statement of research findings with quantitative data and statistical analysis; (4) Conclusions: interpretation of the meaning of the results. A **method/device evaluation** abstract *must* include (1) Introduction: identification of the method or device and its intended function; (2) Method: description of the evaluation in sufficient detail to permit judgment of its objectivity and validity; (3) Results: findings of the evaluation; (4) Experience: summary of the author's practical experience *or* a notation of lack of experience; (5) Conclusions: interpretation of the evaluation and experience. Cost comparisons should be included where possible and appropriate. A **case report** abstract *must* report a case that is uncommon or of exceptional teaching/learning value and must include: (1) patient data case summary and (2) significance of case. Content should reflect results of literature review. The author(s) should have been actively involved in the case and a case-managing physician must be a co-author or must approve the report.

Abstract Format and Typing Instructions

Accepted abstracts will be photographed. First line of abstract should be the title in all capital letters. Title should explain content. Follow title with names of all authors (including credentials), institution(s), and location. Underline presenter's name. Type or electronically print the abstract *single spaced in the space provided on the abstract blank.* Insert only one letter space between sentences. Text submission on diskette is encouraged but must be accompanied by a hard copy. Identifiers will be masked (blinded) for review. Make the abstract all one paragraph. Data may be submitted in table form *and simple figures may be included provided they fit within the space allotted. No* figures, illustrations, or tables are to be attached to the abstract form. Provide all author information requested in right column of abstract form. A clear photocopy of the abstract form may be used. Standard abbreviations may be employed without explanation. A new or infrequently used abbreviation should be preceded by the spelled-out term the first time it is used. Any recurring phrase or expression may be abbreviated if it is first explained. Check the abstract for (1) errors in spelling, grammar, facts, and figures; (2) clarity of language; (3) conformance to these specifications. An abstract not prepared as requested may not be reviewed. Questions about abstract preparation may be telephoned to the editorial staff of RESPIRATORY CARE at (214) 243-2272.

Deadlines

Deadline Allowing Revision

Authors may choose to submit abstracts early. Abstracts received by March 5 will be reviewed and the authors notified by April 22. Rejected abstracts will be accompanied by a written critique that should in many cases enable authors to revise their abstracts and resubmit them by the final deadline (May 28).

Final Deadline

The mandatory Final Deadline is May 28 (postmark). Authors will be notified of acceptance or rejection by *letter only*— to be mailed by August 15.

Mailing Instructions

Mail (Do not fax!) 2 clear copies of the completed abstract form and a stamped, self-addressed postcard (for notice of receipt) to:

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- ❑ AARC Position Statement

RESPIRATORY CARE

December Reader Service **Expires March 31, 1994**

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80	81	82	83	84	85	86	87	88	89	90	91	92	93	94
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170	171	172	173	174	175	176	177	178	179	180	181	182	183	184
185	186	187	188	189	190	191	192	193	194	195	196	197	198	199

I. Type of Instn/Practice
1 ❑ Hosp ≥ 500 or more beds
2 ❑ Hosp 300 to 499 beds
3 ❑ Hosp 200 to 299 beds
4 ❑ Hosp 100 to 199 beds
5 ❑ Hosp <100 or less bed
6 ❑ Skilled Nursing Facility
7 ❑ Home Care Practice
8 ❑ School

II. Department
A ❑ Respiratory Therapy
B ❑ Cardiopulmonary
C ❑ Anesthesia Service
D ❑ Emergency Dept

III. Specialty
1 ❑ Clinical Practice
2 ❑ Perinatal Pediatrics
3 ❑ Critical Care
4 ❑ Clinical Research
5 ❑ Pulmonary Function Lab
6 ❑ Home Care/Rehab
7 ❑ Education
8 ❑ Management

IV. Position
A ❑ Dept Head
B ❑ Chief Therapist
C ❑ Supervisor
D ❑ Staff Technician
E ❑ Staff Therapist
F ❑ Educator
G ❑ Medical Director
H ❑ Anesthesiologist
I ❑ Pulmonologist
J ❑ Other MD
K ❑ Nurse

V. Are you a member of the AARC?
1 ❑ Yes 2 ❑ No

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